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# ANNALS OF INTERNAL MEDICINE

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## OUR CHANGING VIEWPOINT ABOUT CONGESTIVE FAILURE \*

By ISAAC STARR, *Philadelphia, Pennsylvania*

### INTRODUCTION

My old friend "Pete" Abbott, whose untimely death at the height of his powers at the age of 41 was one of the tragedies of American Medicine, used to say that there should be three kinds of scientific papers. In the first the author recounted new facts as he had observed them and drew appropriate conclusions. Papers of this type fill the American medical literature. In the second the author reviewed the literature and this type is also common. But Abbott was conscious of the lack of papers of a third type that he considered equally desirable, a type in which the primary interest is in ideas rather than in facts, and in which the author marshals the evidence which leads him to these beliefs. Papers of this kind are rare in the American literature. Perhaps this is what a most discerning critic, Professor Krogh of Copenhagen, had in mind when he wrote, after visiting this country in 1946; "There is, as I have had occasion to observe, practically no possibility of getting a fairly large, closely reasoned paper published in the United States."

This presentation is emphatically of the third type; I have no new facts to offer for your consideration and I do not intend to review the literature at length. But my ideas about congestive heart failure have been changing. The faith of my fathers, by which I facetiously mean the body of belief about congestive failure taught me in the medical school, has been lost to me, and I can subscribe to it no longer. As doctors must have a system of beliefs if they are to treat their patients logically I am struggling for a new credo, and not altogether satisfied with it. But doctors with patients before them, unlike those engaged in pure science, are constantly being forced to come to an immediate decision, and before we can act thoughtfully and logically, a conception of what is really wrong with the patient is essential.

\* Read at the San Francisco meeting of the American College of Physicians, April 21, 1948.



So, without further ado, I will tell you why I can hold the older conceptions no longer, and of my struggles to reach a new viewpoint. And let me say at once that as my views changed they have become more hopeful. Our failures of therapy in the past may well have been due to misunderstanding of the true nature of the process. Our therapeutic efforts today are much more successful than they were 20 years ago. If we keep our wits about us, and are not afraid of novel ideas and hard thinking, I do not doubt that we will do even better in the near future.

Congestive heart failure is a complex of symptoms and signs which are so familiar that it needs no description to an audience such as this one. The subject could be approached from a number of viewpoints. To those of the descriptive school, heart failure is a group of symptoms and signs; to those of the pathological school, the interest is in the findings at necropsy. But I do not propose to dwell on these viewpoints here, as I myself belong to a new school which is arising and which might well be called the physiological school. I look on heart failure as a physiological process gone wrong and I propose that we consider it from this viewpoint.

Let us concentrate our attention on the cardinal feature which gives the condition its name, the congestion of the greater veins. The veins stand out, swollen with blood and the increased pressure within them can be recognized by palpation alone and measured accurately by any of several methods. The purpose of this lecture is to try to answer several simple questions about this venous congestion, such as: where does the extra blood which over-fills the veins come from, what raises the venous pressure, and especially, what is the relation of this venous congestion to cardiac function? People have been asking these questions for many years so let us start by examining the views held by our predecessors.

One of the oldest and most popular explanations is generally known as the "Dam and Stream Analogy." Described by James Hope in 1842,<sup>1</sup> the Dam and Stream was pictured in Wenckebach's book<sup>2</sup> published in 1937, so the view still underlies the thinking of countless doctors. The blood in the great veins is likened to a pond before a dam in a flowing stream. The heart is thought of as a pump to lift water over the dam. If the heart weakens more water runs into the pond than is pumped out and the pond's level rises.

A second classic experiment was that of Cohnheim,<sup>3</sup> who injected oil into the pericardial sac of dogs to handicap the heart, and found that the venous pressure rose.

A third important factor in forming medical opinion was the behavior of the simplest form of a circulation schema,<sup>4</sup> like that illustrated in figure 1. In such a schema if, after pumping hard, one pumps more weakly, the venous pressure rises.

The fourth factor was the behavior of the Starling heart-lung preparation,<sup>5</sup> in which these organs were isolated from the rest of the animal in such

a fashion that the heart would continue to beat for hours, pumping blood past a resistance into a reservoir from which it flowed down to the heart once more. In this preparation as the heart weakens, the pressure in the veins next to the heart, or rather in the tubing which represents them, rises.

The results of these experiments were judged to be concordant and from them was derived a viewpoint so widely held that I always think of it as the classic view. It may be briefly stated thus: A weakening heart is unable to pump the blood from the veins to the arteries in sufficient amount, therefore

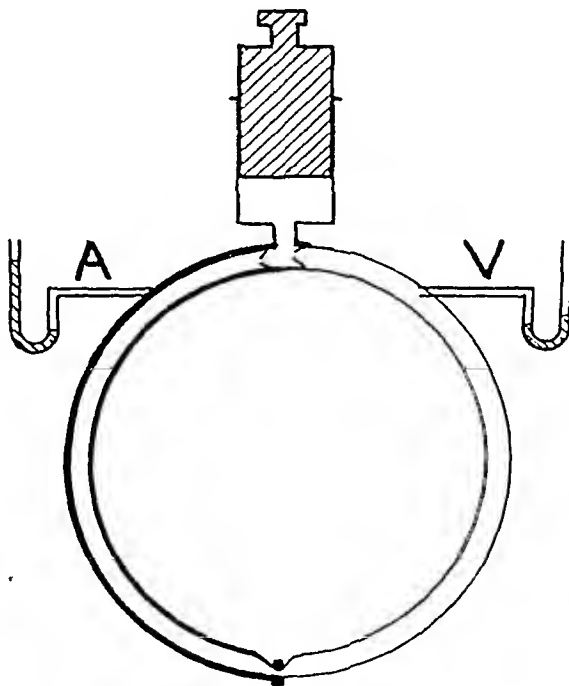


FIG. 1. The simplest form of circulation schema. a. First let us study its behavior as shown. Before the pump is started a pressure of 10 mm. exists throughout the system, this is the static pressure. When one pumps hard the pressures become  $A = 120$ ,  $V = 4$ . When one pumps weakly, the pressures become  $A = 70$ ,  $V = 8$ . Increasing the resistance at the pinchcock increases arterial pressure but always diminishes venous pressure simultaneously, decreasing resistance has the opposite effect. Increased venous pressure together with a maintained arterial pressure cannot be brought about by either weakening the pump, changing the resistance or any combination of the two. b. Let us now inject more water into the system. This lodges chiefly in the most distensible parts, that is, the "veins." The static pressure is now 20 mm. After beginning to pump  $A = 120$ ,  $V = 15$ . Increased venous pressure in the presence of a normal arterial pressure is now attained.

more blood runs into the veins than is pumped out, so the veins become congested and the pressure in them rises. This view has an important corollary: The height of venous pressure is a measure of cardiac strength and weakness, for there was thought to be a direct mechanical relation between the two. Many, probably the majority of doctors, hold this view today. I was taught it with great confidence but I must warn you now that I can hold it no longer.

All this reasoning was done before methods for measuring cardiac output

were available and when these were first applied to the problem discrepancies were soon encountered. The classic view led to the expectation that when the veins were congested the cardiac output would be below normal. And, indeed, on the average this was found to be true.<sup>6</sup> But there were many discrepancies in individual cases; some cases in congestive failure had cardiac outputs estimated to be above normal, and there were many cases of coronary heart disease, hypothyroidism and other conditions which had extremely low cardiac outputs but no venous congestion. Therefore, students of this subject could hold to the classic view only by doubting the accuracy of the estimation of cardiac output, a position that became more and more difficult as these methods were improved; or they could seek for a new theory of congestive failure. Two suggestions can be mentioned at this point; the first view, backed especially by Harrison,<sup>6</sup> sought to explain congestion with a normal circulation by regarding congestive failure as due, not to a diminished cardiac output, but to a disproportion between the strength of the two sides of the heart, peripheral venous congestion being attributed to right heart failure, pulmonary congestion to left heart failure. I cannot support this view myself for reasons which will appear later. The second view was put forward by Altschule<sup>7</sup>; it considered congestive failure to be due to a disproportion between the cardiac output and the metabolic demand for oxygen, and emphasized that congestion with a normal cardiac output occurred when the metabolic rate was elevated. Later work<sup>8,9</sup> has shown that this is sometimes, but by no means always, true. So, not satisfied by these explanations I was attracted into the field, but before I recount the results of my own studies, let me criticize briefly the evidence which led to the classic viewpoint.

In the Dam and Stream Analogy there is no circulation, a source of power up-stream is assumed. A closer, though still very imperfect analogy is secured by turning the pump up-stream so that its output flows into the pond again, its only source of supply. Under these circumstances one sees at a glance that the rate of pumping would have no effect whatever on the water level of the pond.

In Cohnheim's experiment<sup>3</sup> of cardiac tamponade the venous pressure rose but the arterial pressure fell. This difference from clinical congestive failure did not attract attention because it was universally believed that the arterial pressure fell in clinical congestive failure until about 1905 when the blood pressure was first measured in this condition. But in Landis' somewhat similar experiments,<sup>10</sup> arterial blood pressure was maintained, and I do not doubt this would be a profitable field for further exploration.

In the heart-lung preparation, the venous pressure is dependent on the height of the reservoir. When the heart weakens and stops, its filling pressure must rise to equal the reservoir height. And because the operator keeps the reservoir full, adequate cardiac filling is assured. But there is no assurance of adequate cardiac filling in the intact animal, nor is there any mechanism to support venous pressure as the open reservoir does.

To me, therefore, there was nothing compelling in the evidence which had been offered to support the classic viewpoint. And, as certain clinical observations had made me doubtful of its correctness, I determined to study the subject. As a beginning it seemed wise to study a mechanical model to assure myself that I had a grasp on the purely mechanical factors. Therefore, with the help of Rawson, a model was designed<sup>11</sup> whose pumps behaved in accordance with Starling's law of the heart, and which had both a systemic and a pulmonary circulation. Let me describe its behavior, as simply as I can, and let us ask ourselves what alterations in its behavior will cause it to simulate the pressures found in congestive failure.

First let us consider the *volume changes* of the blood which congests the veins, and ask ourselves where this extra venous blood comes from. The model shows that more than one factor may be at work, and not all the factors are concerned with the heart. We have:

### I. Factors dependent on the heart

- a. When the pumps are weakened and the circulation slows, the blood which congests the veins comes *from the arteries*.
- b. When one pump is weakened relative to the other but the circulation maintained, the circuit before the weakened heart gains blood *from the other circulation*. In these two examples the transfer of blood is caused by a change in cardiac function, so I think of them as the *cardiac factors* in the production of venous congestion.

### II. Factors independent of cardiac strength or weakness.

- a. If peripheral resistance is diminished by loosening the pinchcock, the veins are congested with blood *from the arterial side*.
- b. If vessels of part of the circulation are compressed from without, blood is driven out of the narrowed parts into the more distensible places, that is into the veins.
- c. If the vessels, other than the veins, should actively constrict, the effect would be the same as b, to drive fluid from the narrowed vessels into the distensible veins.
- d. When extra fluid is injected *from without* it collects chiefly in the most distensible parts, that is in the veins.

Certainly it is easy to demonstrate in a model that the veins may become congested, irrespective of the condition of the heart, which might be beating strongly, weakly or not at all, and so we have *extra-cardiac factors* in the production of congestion. These factors have been summarized in table 1.

TABLE I

#### Factors in the Production of Peripheral Venous Congestion

##### I. Cardiac

- a. *Diminished Output*—The excess venous blood comes from the arterial side.
- b. *Weakening Right Side*—The excess venous blood comes from the pulmonary vessels.

## II. Non-cardiac

- a. *Decreased Peripheral Resistance*—Blood transferred to veins from the arterial side.
- b. *Pressure on Vessels from Without*—Blood transferred to the veins from the compressed vessels.
- c. *Active Constriction of Vessels*—Blood transferred to veins from the constricted vessels.
- d. *Increased Blood Volume*—The excess blood accumulates chiefly in the most distensible vessels, i.e. in the veins.

When venous congestion is produced by the last three extra-cardiac factors, it is associated with an increase in the static pressure, a term with which clinicians are usually unfamiliar. The conception behind it I wish to emphasize. The static pressure is the pressure which would exist throughout any circulation when the pump is not working. When one starts the pump of a circulation schema the arterial pressure goes above, the venous below the static pressure. Thus an increase in static pressure raises pressures all around the circulation but this increase is most conspicuous where the pressures are lowest, that is in the veins.

Much of this presentation will be a discussion of the relative weight of these cardiac and extra-cardiac factors in various clinical conditions.

Now let us examine the *pressure* changes when the pump is weakened. In a simple mechanical model (figure 1), when one, after pumping vigorously, pumps more weakly, the pressure in the veins rises, as has long been known. But the pressure in the arteries falls simultaneously and so the pressures that result are not like those of congestive failure as we see it in the clinic, for in these cases the venous pressure is elevated but arterial pressure is maintained. Attempts to reproduce this combination in a schema by weakening the pump, altering the peripheral resistance, or by any combination of both, all fail; any change which puts venous pressure up, puts arterial pressure down and vice versa.

To produce the pressure pattern found in clinical congestive failure one must alter the pressure of the system at rest, the static pressure. This can be readily done by injecting more fluid into the system. Then by starting the pumps we can readily secure the combination sought, a high venous pressure and a normal arterial pressure, as we see so often in the clinic. Raising the static pressure by pressing on the tubing from without accomplishes the same effect.

One is, therefore, unable to reproduce the pressure relations of clinical congestive failure by weakening the "heart," but one does it readily by injecting fluid from without, or by "vasoconstriction." So the results of these experiments point away from the heart and towards other factors in the circulation as the most important cause of venous congestion. These leads were followed up in animal experiments.

## ANIMAL EXPERIMENTS

Although it was well known that the venous pressure of the heart-lung preparation rose as the heart weakened I could find no record that the

crucial experiment had been done in the intact animal, and while my experience with the schema was fresh in my mind, an observation, made during an experiment designed for another purpose, made me resolve to undertake a direct attack. In order to produce abnormalities of form of the ballistocardiograph by directly damaging the heart, I had prepared anesthetized dogs with the chest open, and attacked the right ventricular wall with a cautery until I had almost completely destroyed it; and I was no little surprised to find that only a negligible rise in venous pressure accompanied the maximum damage to the right heart that I knew how to inflict. Therefore the aim of this experiment was changed and it was repeated on other animals by Meade, Jeffers and myself.<sup>12</sup> Also, after losing many animals, we produced as large an infarct in the right heart of a dog as permitted recovery, and followed the venous pressure for 12 weeks without finding any elevation.

The onset of war cut short our experiments but this unexpected result attracted other investigators into the field. In an experiment much similar to ours, Bakos<sup>13</sup> obtained the same results. In a series of experiments, reported as yet only in abstract, Smith and Roos<sup>37</sup> were unable to produce venous congestion in 5 dogs by coronary ligations or widespread coronary embolism with potato starch, but when they first increased blood volume by transfusion, similar cardiac damage resulted in elevated venous pressure and dilatation of the heart with other signs of acute heart failure. Landis et al.<sup>10</sup> damaged the heart by ligature of coronary vessels and by inducing auricular fibrillation without producing a rise of venous pressures higher than controls when the animals were at rest. However, when they were exercised, by electrical muscular stimulation the venous pressure of the "cardiac" animals was higher than that of the controls but, unlike patients with congestive failure, as soon as exercise had ceased the venous pressure fell to normal levels once more.

Landis et al.<sup>10</sup> also tried cardiac tamponade and the results came close to what we see in the clinic in cases of constrictive pericarditis. In these experiments the venous pressure rose, as indeed it must if life is to continue, for blood must be forced into the compressed heart against unusual resistance. The relation of these results to clinical congestive failure is not clear to me.

Therefore, it appears that congestion of the veins has not yet been reproduced by direct damage to the heart alone in resting animal preparations although it has by tamponade. Perhaps one should not say it cannot be produced by damaging the heart, but an attempt to produce it by other methods was plainly indicated.

As clinical congestive failure could be simulated in the model by injecting fluid into the circulation, I tried intravenous injections in animal experiments, a field in which many others had preceded me.

In my experiments<sup>14</sup> large intravenous injections of acacia solution elevated venous pressure markedly and if the animal was then killed the "static" pressure was found to be elevated also. So for a time after such

injections the animals had the increased blood volume and the increased venous pressure of congestive failure and after death the increased static pressure also, but they had nothing organically wrong with their hearts.

I cannot, however, claim to have reproduced clinical congestive failure in these experiments because the increase of venous pressure after large intravenous injections was temporary. Perhaps because the injected fluid leaves the vessels, perhaps because the veins slowly dilate to accommodate the extra volume, the venous pressure falls as soon as the injection is stopped, rapidly at first and then more slowly. Landis<sup>10</sup> obtained similar results with whole blood and with Ringer's solution but in one dog he produced a sustained rise of venous pressure after an intravenous injection, a fact which means to me that more work is needed in this field. But I must emphasize the similarity of the condition of animals soon after large intravenous injections to the clinical condition now being called high output failure.

A third method of producing high venous pressure in animal experiments is by asphyxia<sup>15, 12, 10</sup> and, as arterial pressure, cardiac output and venous pressure are all elevated together, we have the right to believe that the effect is due to a widespread vasoconstriction of veins as well as arteries. Whether there is analogy here to anything seen in the clinic is an interesting question.

So we leave the animal experiments with a viewpoint much similar to that obtained from the circulation schema. Increased venous pressure at rest may be caused by contraction of blood vessels, and by increased blood volume, even though the heart is organically sound; and it follows cardiac tamponade as it must if the heart is to be filled at all. But direct damage to the heart muscle of an intact animal does not cause it as long as the animal is at rest, and therefore increased venous pressure at rest is not the direct consequence of cardiac weakness.

Now I am not a person who has great confidence that the results obtained in acute animal experiments can be directly applied to clinical problems so, without too much bias, let us survey the problem from the clinical viewpoint and discuss the experiments and observations made in the clinic.

### CLINICAL EXPERIMENTS

Some of the experiments I did on animals can be performed in the clinic. The effect of intravenous injection of large amounts of saline and of 5 per cent human albumin solution into volunteers was studied by Warren et al.<sup>16</sup> The results were quite similar to expectations from the animal experiments. Right atrial pressure was elevated immediately after the injection in all instances, to a maximum of 19 cm. H<sub>2</sub>O in one case, but the high value was never sustained. Nevertheless, about one hour later this pressure was still considerably above the value found before injection in all subjects given albumin. Again we have evidence that venous pressure can be elevated by increasing blood volume although the heart is normal and the cardiac output at or above the normal level.

The fact that the pressure changes characteristic of congestive failure were produced in a mechanical model only by elevating the "static" pressure, naturally led me to attempt to measure "static" pressure in the clinic.<sup>14</sup> There seemed only one way of doing this: wait until the heart stopped at death and then promptly measure the pressure prevailing throughout the vascular system. This fell off slowly immediately after cessation of cardiac action but a plateau was soon attained and the values secured here in a series of patients are recorded in a previous publication.<sup>14</sup> In those dying in congestive failure the static pressure is elevated sufficiently to account for most, but not all, of the increase of venous pressure found in such cases during life.

These results demonstrate that the larger part of the pressure difference between those with venous congestion and those without it is not due to differences of cardiac action, for with cardiac action out of the picture the differences persist. In our search for the cause of the increased venous pressure in congestive failure, we must look for a factor which persists after the heart has ceased to beat. Again we are led away from thinking of cardiac dysfunction as the immediate cause of the major part of the venous congestion.

The work of two other groups provides an interesting approach to certain aspects of the problem. If venous congestion is due to fluid retention and edema, then edema and gain in weight would precede the increase in venous pressure, but if the increased venous pressure were the first step, then this should occur before edema.

In Stead's clinic,<sup>17</sup> patients who could be kept out of congestive failure by regular injections of mercurial diuretics were followed carefully when the drug was withheld; and edema and weight gain preceded the rise in venous pressure, results which support the view which best fits my own evidence. However, by Reichsman and Grant<sup>18</sup> in Harrison's clinic, a similar type of investigation was carried out on patients dependent on digitalis to keep them out of the congestive state. When this drug was withheld, a rise in venous pressure preceded edema and gain of weight, quite the opposite result from that secured when the mercurials were withdrawn.

Reichsman and Grant<sup>18</sup> suggest that the results of Warren and Stead<sup>17</sup> might be explained by assuming that the latter's patients were dehydrated by the preceding course of mercurial diuretics when the test was begun. But I have frequently observed edema to occur in cardiac patients before any venous congestion was detectable by the usual clinical tests, and many of these patients had had no course of diuretics, so I doubt if this is the explanation. Certainly the field needs further study. Very few patients have been studied so far and when venous pressure is measured simultaneously in both arms of a single subject, the difference in result is sometimes greater than is usually realized. This is a field that any clinician could attack, as no especial apparatus or technic would be required and I hope that data on the important point will be accumulated rapidly.



The results secured after the withdrawal of digitalis<sup>18</sup> are consistent with McMichael's contention that the primary effect of this drug is to cause relaxation of veins. If this view is correct, the results from Harrison's clinic<sup>18</sup> are not inconsistent with the view that the cardiac factor in congestive failure is a small one.

### CLINICAL FACTS CONCERNING CONGESTIVE FAILURE

Before attempting to develop further my ideas on this subject, let us consider together the facts clinicians have gleaned by years of observation of cases of congestive failure, because I judge facts so acquired to be in no wise inferior to those obtained by experiment.

So I propose to state several facts bearing on the problem and then to discuss their meaning. I think these statements are so self-evident that there is no danger of any one of my readers disagreeing with them.

1. *Congestive failure occurs with great frequency in persons with damaged hearts.* This fact is the foundation stone of the view that cardiac damage is the prime cause of congestive failure. It is indeed evidence of the strongest kind but it throws no light on the nature of the relationship. The long interval between the original cardiac damage and the development of congestive failure suggests that the relationship is not an immediate and direct effect.

2. *Digitalis benefits many cases of congestive failure.* To most people the clinical improvement is due to improvement in cardiac function caused by the drug, and that the drug can improve cardiac function in certain conditions of disease seems well established. But we were all taught to give the drug to a case of congestive failure until we obtained a diuresis and certainly great benefit often followed quickly the establishment of this diuresis, so the improvement might be due to fluid loss. McMichael<sup>19</sup> has brought forward evidence that digitalis relaxes the veins, and this action may well afford an explanation for the rapid fall of venous pressure that follows the intravenous injection of the purer preparations.<sup>34, 35</sup>

3. *Examination of the heart at necropsy does not disclose whether the patient died in congestive failure or not.* We have no pathologic evidence which indicates the nature of the relation between congestive failure and heart disease. Thus in Gore's analysis of 143 cases of diphtheritic myocarditis demonstrated at necropsy,<sup>20</sup> congestive failure occurred in only 34 per cent while the majority, 51.4 per cent suffered terminally from a shock-like condition with hypotension, weak thready pulse and imperceptible heart action.

4. *The heart can be severely damaged, as by myocardial infarction, by tumor, or by lesions affecting the muscle and venous congestion does not necessarily follow.* I am sure that instances of this kind are within the experience of every one. I mention it only to emphasize that there is no necessary relationship between venous congestion and manifest cardiac damage.

5. *Most people die without congestive failure.* It seems to me this self-

evident fact has never had the attention it deserved. If diminished cardiac output is the cause of the venous congestion every dying person should show it as the heart's function must diminish before it stops in death. But most persons die without venous congestion so we must conclude either that the cardiac factor is not of sufficient importance to produce manifest congestion of the veins, or that this effect is regularly overcome by another physiological mechanism, such as a general relaxation of vessel tone, which must be assumed to occur as death approaches except when the patient has congestive failure. Regarded in either way it is evident that the cardiac factors are of less importance than the extra-cardiac factors.

6. *Mercurial diuretics greatly benefit patients with congestive failure.* This fact seems to me inconsistent with the classic view. When diuresis followed the exhibition of digitalis or the xanthenes, one could properly argue that the renal action was secondary to a cardiac effect. But the mercurials depress the heart in any concentration known to affect it at all. Lowering of venous pressure, relief of orthopnea and other symptoms promptly follow the action of a drug with no known cardiac effect in the concentration employed. Here again we are led away from the heart in our search for an explanation.

7. *Restriction of Na intake benefits patients with congestive failure.* This fact, together with the benefit occurring from diuretics makes one suspect that the essential thing is to rid the patient of fluid and to prevent its reaccumulation.

8. *In patients in or threatened with failure, pressure over the liver will distend the neck veins.* I mention this fact, it is sometimes used as a test on the continent of Europe, because it demonstrates so clearly that peripheral factors rather than cardiac may exercise the chief control over the height of venous pressure. Certainly the heart's potential strength does not change when one presses over the liver and when the pressure is released, but the venous congestion does. The venous pressure, therefore, is no reliable index of cardiac strength or weakness.

## DISCUSSION

It is so much easier to be a destructive than a constructive critic that from my point of view there is much to be said in favor of stopping my presentation at this point. For the old concept that the increased venous pressure was the direct mechanical consequence of cardiac weakness and so a measure of it, seems gone beyond reclaim. But the building of a better conception is another matter. Let us not shirk it, however; indeed we dare not, for patients are dying of congestive failure daily, perhaps due to our ignorance. So let us try to be constructive, not with the idea that our theory will be perfect, but with the expectation that it will be closer to the truth than the conceptions we feel forced to abandon. Let us start by trying out several simple ideas presented as questions.

it is apparently not sufficient. And were plethora the sole cause, bleeding should cure congestive failure. That it helps some cases is evident, but it is certainly not curative. There must be other factors in the situation.

*Is fluid retention the cause of the picture?* Excess fluid within the elastic envelope of the skin would press on adjacent blood vessels from without, squeezing the blood into the more distensible parts of the vascular system, and increasing the pressure and congestion of the veins. It is entirely possible that the picture could be explained this way. The most weighty argument in favor of this view is the striking clinical improvement that occurs in so many of these patients when fluid and its contained salts are removed by diuresis, tapping the chest or abdomen, or Southey's tubes. The fall in venous pressure after removal of fluid is often striking. And this conception also provides explanation for the persistence of the pressure elevation after death.

The chief objection to this line of thought will occur to most of you immediately. In many patients with nephrosis we have great retention of fluid but no congestive failure. I suspect this difference to be due to a small blood volume in cases with nephrosis,<sup>30</sup> an adaptation to the great loss of serum albumin into the urine, so that the blood pressed out of the small vessels by pressure from without does not over-fill the great veins.

I would like to digress here to consider another objection that might occur to some. I was taught with great confidence that edema of renal origin was readily distinguished from that of cardiac origin; the first involved the eyelids and face; the latter spared these parts to be concentrated in the dependent parts of the body. It is my opinion that this distinction is not valid evidence of the genesis of edema, and that the difference can be more readily explained in another way. All edema is subject to gravity and the fluid tends to collect where tissue tension is low. Edematous cardiac patients are usually orthopneic and keeping the head up prevents edema from accumulating around the eyes. The nephrotic patient lies flat and fluid accumulates there. I have seen occasional cardiac patients who had edema but not orthopnea; these developed edema of the face when they lay flat. I have also taken a patient with nephrotic edema and made him sleep with the head elevated, and the edema soon left the face and its distribution then resembled that taught as characteristic of heart disease. So I do not believe that a real difference between the clinical characteristics of edema of renal and of cardiac origin has been demonstrated.

*Is venous constriction a factor in the congestion?* I do not know how to answer this question and I have often thought that a young man might profitably spend his life studying the veins in clinical conditions. We lack a simple clinical method. Arterial pressure is a good indication of arteriolar tone because when the arterioles contract the heart responds to the situation by increasing its work so cardiac output tends to be maintained and arterial pressure to rise. But on the venous side the situation is different: if venous

pressure rises, the cardiac output tends to increase according to Starling's law. Hence if the veins contract the heart may act to keep the pressure from rising and so venous pressure alone is a poor indicator of venous tone. But knowledge of venous pressure and cardiac output would permit an estimation of venous tone, and our knowledge of this subject is just beginning. Employing this method, McMichael<sup>19</sup> concluded that diminution of venous tone accounted for the fall of venous pressure seen in cases of congestive failure when pure digitalis preparations were given intravenously but he made this test on relatively few cases, and his contention that digitalis has no direct cardiac effect is contrary to expectations from pharmacological experiments on the isolated heart. But if one assumes that differences of venous tone do occur in patients, we have a simple explanation for some of the discrepancies we see. Thus, diminished venous tone is an obvious explanation for the failure of some cases with increased blood volume to exhibit high venous pressure, and increased venous tone is a reasonable explanation for that fraction of the elevated venous pressure of congestive failure not accounted for by the elevation of static pressure measured after death.

*Are changes in peripheral resistance a factor?* Loosening the pinchcock causes the veins to gain fluid in the model, but the arterial pressure falls. Certainly this mechanism is not a factor in most cases of congestive failure as the arterial blood pressure is characteristically maintained. The great majority of such cases have cardiac outputs either normal or below, and arterial blood pressures either normal or elevated. We cannot think of peripheral vasodilatation in these, indeed, the evidence strongly points to peripheral constriction in most of them. Let us remember that peripheral resistance might be elevated in two ways: by a pinchcock-like effect, which would greatly increase resistance but diminish lumen very little and so displace little blood; and by a widespread narrowing of vessels which would increase resistance and displace blood at the same time. The latter may well be a factor in the venous congestion of congestive failure.

We can therefore identify several factors which may play a part in the production of venous congestion but the evidence suggests that each one of them acting alone may be insufficient to cause congestive failure. Perhaps this was to be expected. In the normal subject the veins are in part collapsed and a considerable quantity of blood may be added with little, if any, increase in the pressure within them. We learn this daily when giving transfusions. But once the veins are full, the addition of small amounts of blood would be expected to result in much larger increments of pressure, and in congestion manifest to clinicians. So it is not surprising that single factors, acting alone, are often insufficient to produce manifest congestion of the veins.

I suggest, therefore, that the venous congestion of congestive failure, as we usually see it in the clinic is due to the effect of more than one of the factors mentioned, and that the combination of factors which produces it may vary from case to case.

In the ordinary case of congestive failure one is compelled to believe that increased blood volume and edema are factors because they are so regularly found; that cardiac factors are present because of collateral evidence of cardiac disease. Changes in venous tone are the handiest explanation for such phenomena as the increased venous pressure of cardiac tamponade, during asphyxia and in the agonal rise in venous pressure sometimes seen in the clinic. So the evidence indicates that while the cardiac factor is too small to produce noteworthy venous congestion by itself in resting subjects, acting in conjunction with these other factors it may play a larger part. And even though of small importance during rest, in exercise the cardiac factor increases in effectiveness<sup>10</sup> because, due to the pumping action of the working muscles, more blood may indeed be pumped into the veins than is pumped out by the weakened heart.

However, to some, such reasoning may seem to be beside the point. Although there may be a reasonable way to account for venous congestion with little, if any, mention of the heart, yet one of the most obvious facts about the situation is that congestive failure occurs chiefly in patients long

TABLE II

## A Suggested Train of Events Leading to Congestive Failure

1. Heart Disease
2. Diminished Circulation to
 

a. Kidney	b. Bone Marrow	c. Other
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3. Retention of Water and Salt
4. Increased Blood Volume
5. Venous Congestion
6. Stimulation of Heart from Increased Filling Pressure
7. Further Damage to Heart

known to have had cardiac abnormality and this is evidence of the strongest kind that heart disease causes congestive failure. I have no intention of denying this and the two conceptions are not inconsistent, if one remembers that causes may be of two kinds, immediate and remote. The facts may be reconciled by thinking in terms of a train of events; I have represented such a train in table 2 and let us now consider it.

I have placed cardiac dysfunction at the top because it so often antedates the congestion. The idea that the train went through the kidney<sup>12</sup> was, of course, suggested by the signs of renal dysfunction, albuminuria, casts, reduced dye elimination, blood urea and nitrogen retention that are so regularly found in congestive failure, and it seemed a short step to conceive that such a damaged organ would not normally eliminate water and electrolytes. And now strong evidence has been secured from Stead's<sup>23</sup> and from Leiter's<sup>24</sup> clinics, using the clearance technics developed by Homer Smith, that the renal circulation is indeed reduced in congestive failure much more than reduction of cardiac output would account for; and there is additional evidence that the elimination of sodium is also much disturbed in such cases.<sup>32, 33</sup>

The idea that the train goes through the bone marrow was suggested by McMichael<sup>25</sup> in 1938 and this view has the advantage of affording a ready explanation for the increased blood volume of congestive failure, because increased blood volume follows exposure of healthy persons to the anoxemia of high altitude.

I mention the possibility of the train going through the endocrine system for two reasons: overdosage of certain adrenal products is well known to cause salt and fluid retention and, in some early experiments apparently not well substantiated, such overdosage was thought to cause a condition akin to congestive failure. And the possibility that the pituitary anti-diuretic hormone plays a part should not be forgotten.

These three routes are not mutually exclusive and from there on the train follows logically enough, but perhaps you will be surprised to note that I have reintroduced cardiac damage at the bottom.

When I was teaching in the course in Pharmacology, we had a student experiment in which, after exposure of the heart for attachment of a myocardiograph, shock was produced by bleeding, and then treated by the intravenous injection of saline and colloidal solutions. Occasionally in an excess of therapeutic enthusiasm, the students would inject saline solution too fast and under too great pressure, with the result that after temporary improvement in its function, the heart dilated and beat feebly; and as instructor in charge, I was forced to intervene to save the experiment by reducing or stopping the intravenous injection, after which the heart soon regained its normal size and beat strongly once more. I have no doubt that everybody who has worked on the isolated or exposed heart of animal preparations has seen it dilate when filling pressure was excessive and Starling made such observations the basis of his Law. To me this experience raises the question whether the increased venous pressure seen so often in the clinic may be a factor in damaging the heart's function by over-distending it.

I do not feel confident that I know the answer to this question and have been searching for relevant facts. Certainly in the clinic we frequently see the heart diminish in size when venous congestion disappears. Doctors have been interpreting this according to the classic view; that is, the venous congestion diminished because the heart's function improved. To me, the alternative view is also possible: the heart diminished in size, and doubtless increased in strength because the venous pressure diminished, just as I have seen the hearts of animal preparations do so often.

I have another reason for introducing heart failure at the bottom of the proposed train of events. When analyzing the relation between congestive failure and the heart, two pitfalls must be avoided. The first when stated baldly sounds naive: The heart must have been affected because the patient died. This viewpoint cannot be laughed off because it points up a distinction which must be drawn before the problem can be visualized clearly. The heart stops beating and the patient is pronounced dead. Obviously, the

heart failed to perform its function of pumping the blood and this failure, absolute in the end, was doubtless preceded by an interval in which it was partial; i.e. the heart beat weakly for a time before it ceased to beat at all. Certainly the heart did fail, but a failure of this type is characteristic of every organ in the body at death. The liver fails at death, but this is not obvious and we are not tempted to diagnose liver disease because of it. But the heart's terminal failure is conspicuous and we are tempted to attribute death to it. In the absence of a clear cause of death clinicians succumb easily to this temptation.

The point is that we must distinguish between primary and secondary effects, if a primary cause is amenable to treatment, the secondary effects take care of themselves. If the secondary effects are corrected, the primary cause remains and the salutary effect is likely to be temporary. This is a most important distinction because on it should be based our efforts at therapy. This paper is a discussion of primary causes of congestive failure with the thought that if it was well understood, treatment would be more effective. Let us not be distracted from our search by the thought that the heart always fails terminally.

The second pitfall is in the old and well known fallacy of the circular argument. Too many doctors, accustomed by training to attribute venous congestion to a weak heart when asked for their evidence that the heart was truly weak are likely to cite the venous congestion. Certainly the evidence already presented convinces me, and I hope you also, that the two are not necessarily associated. You can certainly have a weak heart without venous congestion and, in animal experiments at least, you can have venous congestion without a weak heart. Does the latter occur in the clinic? That is the question before the house.

But if we refuse to accept venous congestion as evidence of cardiac weakness, how are we to identify a weak heart during life, and the answer to this problem is not as easy as some suppose. A history of dyspnea on exertion is relied upon by many but it can also be caused by pulmonary disease or anemia. I think modern clinicians would agree that such evidence as the presence of murmurs, the loudness of the heart sounds, the blood pressure and the palpation of the pulse are of little help; too many irrelevant factors enter into the situation. Fortunately more reliance can be put on other methods.

The electrocardiogram is, of course, the final arbiter in the detection of arrhythmias, and of the greatest usefulness in the detection of local lesions. I have seen no evidence that the minor abnormalities, notching, slurring and T-wave changes have the value which some doctors attribute to them, and certainly no one claims that the electrocardiogram will detect the strength or weakness of the heart.

If you can measure cardiac output you can calculate the heart's work, at least approximately. Here then is a real test of cardiac strength or weak-

ness. These are the methods which hold promise of providing decisive evidence in the future. But we are still in the era of tests made at rest. A diseased heart might be able to perform its work normally while the body rested but be unable to respond properly when more work was demanded of it. While estimations of cardiac output in patients at rest are now becoming commonplace, very few have been reported during or after exercise.

The roentgen-ray is the final arbiter of the size of the cardiac silhouette and if we knew the heart's work as well, we would be in a position to apply Starling's law of the heart as a clinical test of cardiac function.<sup>26</sup> I attempted this as long ago as 1933. Most interesting results were obtained but the methods available at that time were too time-consuming and elaborate for routine use and, although simpler methods are now available, pressures first from the war and later from other duties have prevented me from returning to this field.

Abnormal enlargement of the roentgen-ray silhouette is, of course, important evidence of cardiac dysfunction although one cannot make the distinction between hypertrophy and dilatation and so between strength and weakness. The surprising, and to me unexpected, return to normal of some very large hearts in cases of hypertension relieved by sympathectomy indicates that great enlargement does not necessarily indicate that recovery is impossible.

The course and outcome of the case often appeals to clinicians as being the final arbiter. Certainly in judging the cardiac condition of any case, the development of abnormalities such as arrhythmias and tachycardias, increasing enlargement of the heart and especially repeated relapse after restoration by treatment, should have the attention they rightly deserve. But how tenuous is the relation of such things to cardiac weakness? I think at once of a patient with a history of rheumatic fever who has had very frequent attacks of auricular fibrillation for the last 15 years. Today at the age of 80, to attend the weekly orchestra concert in her balcony seat, she walks up four flights of stairs without a pause and with less dyspnea than is shown by the author walking beside her.

The conclusion of all this might well be that we will have to wait for conclusive evidence on cardiac strength or weakness. But the temptation to postpone decisions must be thrust aside by doctors. The patient waits in the anteroom. In order to be of maximal assistance and to act logically, we must first arrive at a conception of what has gone wrong with him. Let us proceed as well as we can.

Let us attack the problem by boldly accepting the thesis that congestive failure is caused by a train of events outlined and ask ourselves whether this train may be started at other places than its beginning. Can you have congestive failure when the heart is not weak although we concede it might become so late in the course? Let us again ask ourselves a series of questions.



*Can the train be started by a renal lesion?* Let us consider essential hypertension, in which there is a lesion of the arterioles which might, when far enough advanced, diminish renal blood flow and so start the train leading to congestive failure; and in these cases congestive failure is indeed a frequent event. In some of these cases, I do not know what proportion, the cardiac output is within normal limits during the congestion, so there is no evidence that the heart is weak. And often at necropsy nothing wrong is found with the heart except hypertrophy, and how many ingenious explanations have been brought forward to explain how a heart that gave every indication of being stronger than normal, like the hypertrophied muscles of the blacksmith, was in reality weak. Perhaps the explanation is more simple, perhaps these hearts are really as strong as they appear, perhaps it was the renal lesions, which by diminishing the blood supply to the kidney, started off the train of events leading to congestive failure.

But this explanation does not altogether satisfy me. It is logical to believe that hypertension of itself may damage the heart by overwork, and I have evidence that, as if to keep the heart's work normal in the presence of a hypertension, the cardiac output is often reduced,<sup>26</sup> and this would start the train off itself. Obviously, we are dealing with a complex situation, and congestive failure might be produced by more than one way in cases of hypertension.

*Can the train be started by anoxemia per se?* I am much interested in the figures given by Richards<sup>9</sup> for cardiac output in cases with congestive failure due to pulmonary disease, and due to rheumatic heart disease. In the first group the cardiac output was normal, in the second it was much reduced. The blood pressures being similar, we can calculate the heart's work roughly and evidently the cases of rheumatic heart disease have weak hearts while those with pulmonary disease do not.

Let me cite a case from my own series.

#### CASE REPORT

A. G., age 46 in 1948. Between 1940 and 1943 he was exposed to emory dust.

In 1944 he was first admitted with the following findings: Edema of the ankles, cyanosis, dyspnea on exertion. Red blood cells 7.0 to 7.8 mil. Blood pressure 120/85. Roentgen-ray emphysema and cystic changes. Heart normal in size. EKG changes attributed to digitalis. Cardiac output +17 per cent, after bleeding +17 and 22 per cent. Rate 70. He was treated by bleeding and radio-active phosphorus and improved rapidly.

In 1945 he was again admitted in congestive failure. The findings were: Red blood cells 5.7. Roentgen-ray, heart moderately enlarged. EKG changes slightly more pronounced. He was treated by bleeding (5750 c.c. in all), digitalis, and mercurials, with rapid improvement.

In 1946 there were three admissions in congestive failure. Most of the findings were as before. Roentgen-ray, heart transverse diameter 19 cm., chest 30.1 cm. EKG no change. He was treated as before. There was rapid improvement each time.

In 1947 he was in failure again. The findings: Red blood cells 7.5 to 8.0, blood pressure 123/68. His pulmonary function was studied by Dr. Julius Comroe. Oxygen

saturation, arterial blood 63 per cent, breathing  $O_2$ , 98 per cent. Arterial blood  $CO_2$ , 67 mm. Hg (greatly elevated). Respiration 4 liters per min.: normal. Roentgen-ray heart diameter 16.3 cm.; chest 30.1 cm. Cardiac output + 104 per cent. Rate 82. The patient's ballistocardiogram is shown in figure 2. Treated with oxygen inhalations and as before there was rapid improvement.

Apparently pulmonary disease can cause congestive failure without cardiac weakness demonstrable by the tests we now have. So why not consider the anoxemia the prime factor which set the train in motion. However, there is a difficulty which makes me pause. Prolonged residence of normal persons at high altitude causes increased blood volume but congestive failure does not regularly develop, although cardiac cases are well known to

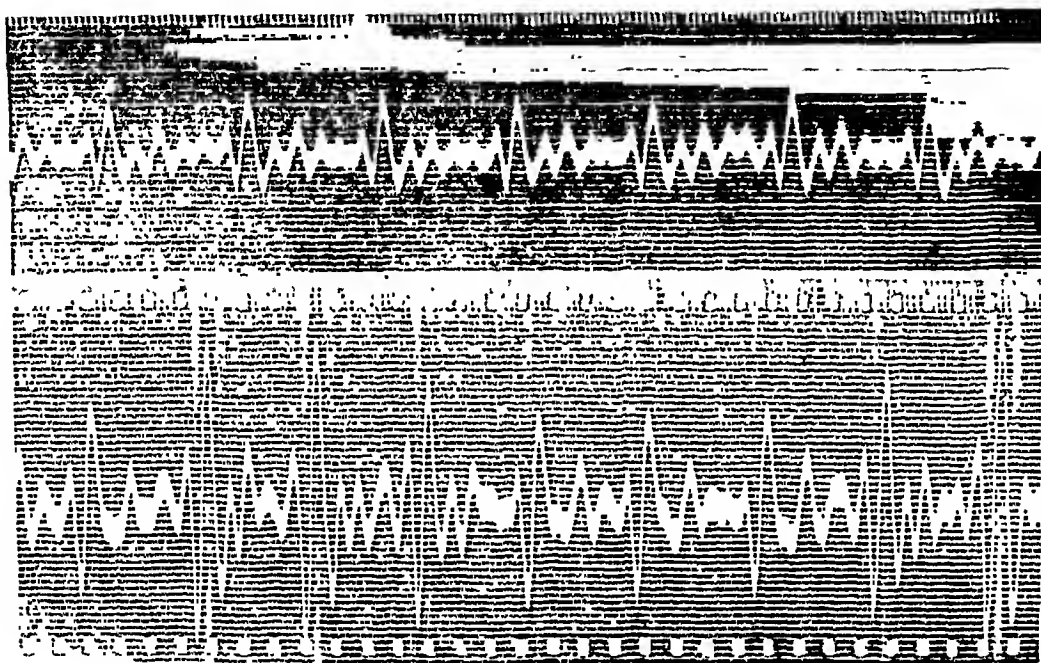


FIG. 2. Ballistocardiograms of a normal subject (*above*—E. P., age 43, 162 lbs.) and of patient A. G. (*below*) described in text. Although he was in congestive failure for the fifth time the patient's impacts are far larger than normal.

do badly at high altitude. Perhaps it is a matter of degree: To obtain anoxemia equivalent to that of my case, one would have to live at an altitude of 22,000 ft. and there are no permanent human habitations above 17,000 ft.

The line of thought suggested by these cases of arterial anoxemia can also be extended to cases of anemia, and perhaps also to cases of hyperthyroidism where the tissue anoxia is not absolute, but relative to the demands for oxygen. In the latter condition congestive failure in the presence of normal or high cardiac output has been reported frequently.

*Can the train be started by fluid retention?* An observation reported by Brozek, Chapman, and Keys can be considered here. Their group of 34 men, normal in all respects before the event, were subjected to a period of semi-starvation, with a daily intake of less than 1,600 calories. The average

body weight fell 23.9 per cent, the basal metabolic rate to — 39.9 per cent. There was edema during this period, but no venous congestion nor dyspnea on exertion. However, during the recovery period with a diet of 2,500 to 5,800 calories, there was a rise in the average venous pressure which in four men reached 15 cm. of saline or more, and dyspnea on exertion became common. One man, released from the experiment after 12 weeks rehabilitation began to eat 7,000 to 10,000 calories per day. Two weeks later he developed edema and dyspnea on exertion and was found to have gained 9 lbs. in the last two days. At this time, the venous pressure was 20 cm. water and the size of the heart had increased sharply. Placed in bed on a diet of 3,000 calories with restricted fluids and ammonium chloride, diuresis soon supervened and he lost 10 lbs. of weight. After this recovery was rapid.

Certainly it is difficult for me to believe that the heart of this subject was weakened by the resumption of food. Is it not much more likely that he simply retained fluid which increased his blood volume, congested his veins and lungs and dilated his heart? After diuresis he was soon normal once more.

The best studied case of beri beri heart disease is that reported by Burwell and Dexter<sup>8</sup> last spring. During the period of venous congestion and acute symptoms, the cardiac output was greatly elevated, over twice the normal resting value, and over twice the value the patient showed after recovering; and when one calculates the heart's work, one finds that this was similarly increased. So here we have congestive failure in the presence of a heart which was not only not weak, but actually beating more strongly than the normal. How was this venous congestion produced? Surely not by cardiac weakness or low cardiac output. Is it not more logical to suppose that it was the retention of fluid which was the primary cause of the high venous pressure and that the effect on the heart was secondary, a stimulation and dilatation such as one sees in the heart-lung preparation when venous filling is excessive?

All of us have been warned that intravenous solutions given too fast or in too large amounts may damage the heart so that the experiment that would prove my point is usually avoided. The best account of it I can find was reported to the Committee on Medical Research in 1945 by Baldwin, Noble, Moore and Richards.<sup>28</sup> In a discussion of the treatment of severe cases of burns by large amounts of saline, plasma and blood intravenously and by mouth they stated "two patients developed an excessively large plasma volume and went into a definitely congestive state with venous pressure of 22 cm. H<sub>2</sub>O." Surely it was the increased plasma volume, rather than any cardiac weakness which was the primary cause of the venous congestion.

So I come to the end of my argument. I cannot think of these cases of fluid retention as having weak hearts in the sense that cases of rheumatic heart disease have weak hearts. And there is another striking difference, the cases of rheumatic heart disease after recovery from failure tend to re-

lapse, but the cases of fluid retention, whether from beri beri or over-administration of fluid, once restored to health can be expected to remain healthy. I cannot think of the two types of congestive failure as similar in their fundamentals. And if you will go with me that far, as I think the evidence is becoming compelling, then the whole field is wide open and everyone must ask himself, how much are these non-cardiac factors entering into the case before me? And so I end on a hopeful note, for these extra-cardiac factors are all more readily treated than the muscular weakness to which congestive failure has been directly and solely attributed. Factors directed to the elimination of fluid are becoming more and more successful in handling these cases, and we are only at the beginning of our knowledge of this subject.

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# ACHLORHYDRIA AND PEPTIC ULCER: A FURTHER STUDY OF THE RÔLE OF PEPTIC ACTIVITY IN THE PATHOGENESIS AND COURSE OF PEPTIC ULCER\*

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## INTRODUCTION

IN 1910 Schwartz<sup>1</sup> enunciated the dictum "no acid—no ulcer" the validity of which has been challenged repeatedly throughout the years. The purpose of this paper is to present a further study on the occurrence of ulcer in acid and non-acid stomachs and, more particularly, on the effect of achlorhydria upon the course of peptic ulcer.

Previous studies<sup>2, 3, 4</sup> have tended to establish the invariable presence of acid gastric juice in patients with chronic peptic ulcer and the absence of ulcer in patients with persistent achlorhydria as in pernicious anemia.<sup>5, 6</sup> Washburn and Rozendaal<sup>7</sup> did not find a single ulcer in 906 cases of pernicious anemia nor did Kahn<sup>8</sup> in 840 such cases. Murphy and Howard<sup>9</sup> noted roentgenologic evidence of duodenal ulcer in four of 440 patients with pernicious anemia; apparently the lesion consisted of roentgenologic deformity (scar) rather than an ulcer crater. Rodgers and Jones<sup>10</sup> have described acute transitory erosions and ulcer seen gastroscopically in patients with histamine achlorhydria; these invariably healed or were absent when re-examined a few days later.

## PEPTIC ULCER AND GASTRIC SECRETION

In active duodenal ulcer the question of achlorhydria or even of a low secretory rate almost never arises. Thus in each of 500 consecutive patients with active duodenal ulcer reviewed by us the maximum response to histamine stimulation was above 40 clinical units (table 1). Very occasional instances of duodenal deformity due to scarring have been noted in patients with pernicious anemia or gastric cancer but we have never seen an active duodenal ulcer under such circumstances.

In gastric ulcer the situation is somewhat different. In 170 cases, nine were reported as achlorhydric after the first stimulation with histamine; in all of these, however, free hydrochloric acid was found in subsequent examinations. The lower secretory rates in this group may be seen by contrasting tables 1 and 2. It is noteworthy that in 20 patients the maximum free acidity, even after histamine stimulation, was less than 20 clinical units;

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

TABLE I  
Maximum Free Acidity—Duodenal Ulcer 500  
Consecutive Cases—First Histamine Test

	No. Cases	Per Cent
Achlorhydria	0	0
1-20 clinical units	0	0
21-40 clinical units	0	0
41-60 clinical units	16	3
61-80 clinical units	54	11
81-100 clinical units	154	31
More than 100 clinical units	276	55
Total	500	100

in one instance the titratable free acidity was only eight clinical units after repeated stimulation and the lowest pH 3.34, a hydrogen ion concentration adequate for the activation of pepsin. It will be recalled that the gastric pH in complete achlorhydria ranges between seven and eight.<sup>11</sup> Thus these findings are consistent with the concept of "peptic" ulceration. It is clear, however, that gastric ulcer may occur not only without "hyperacidity" and "hypersecretion" but with very low concentrations of acid in terms of response to stimulation with histamine.

TABLE II  
Maximum Free Acidity—Gastric Ulcer 170  
Consecutive Cases—First Histamine Test

	No. Cases
Achlorhydria	9*
1-20 clinical units	11
21-40 clinical units	16
41-60 clinical units	32
61-80 clinical units	41
81-100 clinical units	32
More than 100	29
Total	170

\* Subsequent examination disclosed the presence of free acidity in all 9 cases.

### EFFECT OF CONTINUED ACHLORHYDRIA ON THE COURSE OF PEPTIC ULCER

*Surgical Achlorhydria.* Numerous workers<sup>12, 13, 14, 15</sup> have emphasized the importance of obtaining complete anacidity in partial gastrectomy, for postoperative jejunal ulcer almost never develops after resection for gastric ulcer with its lower secretory acid rate, whereas it does develop after resection for duodenal ulcer and particularly so if complete anacidity has not been attained. We have never seen a jejunal ulcer recurrent after partial gastrectomy without a demonstrable pH of less than 4.0.

*Spontaneous Achlorhydria.* It has been our good fortune to observe the fortuitous development of complete achlorhydria in two patients with

gastric ulcer, each of whom has been followed for 10 years or longer and subjected to innumerable roentgenologic and gastroscopic studies as well as histamine tests. In neither case did the ulcer recur after achlorhydria became established. In the first patient, the initial ulcer was acute and did not recur; in the second, a large chronic lesion was present and subsequently recurred at intervals until complete achlorhydria appeared; it then healed and has not recurred.

*Case 1.* Mrs. A. P., a 44 year old woman, was admitted October 10, 1936, because of a burning epigastric distress of four months' duration. A histamine test disclosed a maximum free acidity of 70 clinical units. Roentgen-ray disclosed a small ulceration 4 mm. in diameter in the upper portion of the lesser curvature of the stomach. Gastroscopy failed to visualize the ulcer. The patient was given an antacid ulcer management with relief; the ulcer healed slowly as seen by roentgen-ray, disappearing totally on November 26, 1936. Subsequent histamine tests in the following five years disclosed a decrease in gastric secretion; the ulcer did not recur.

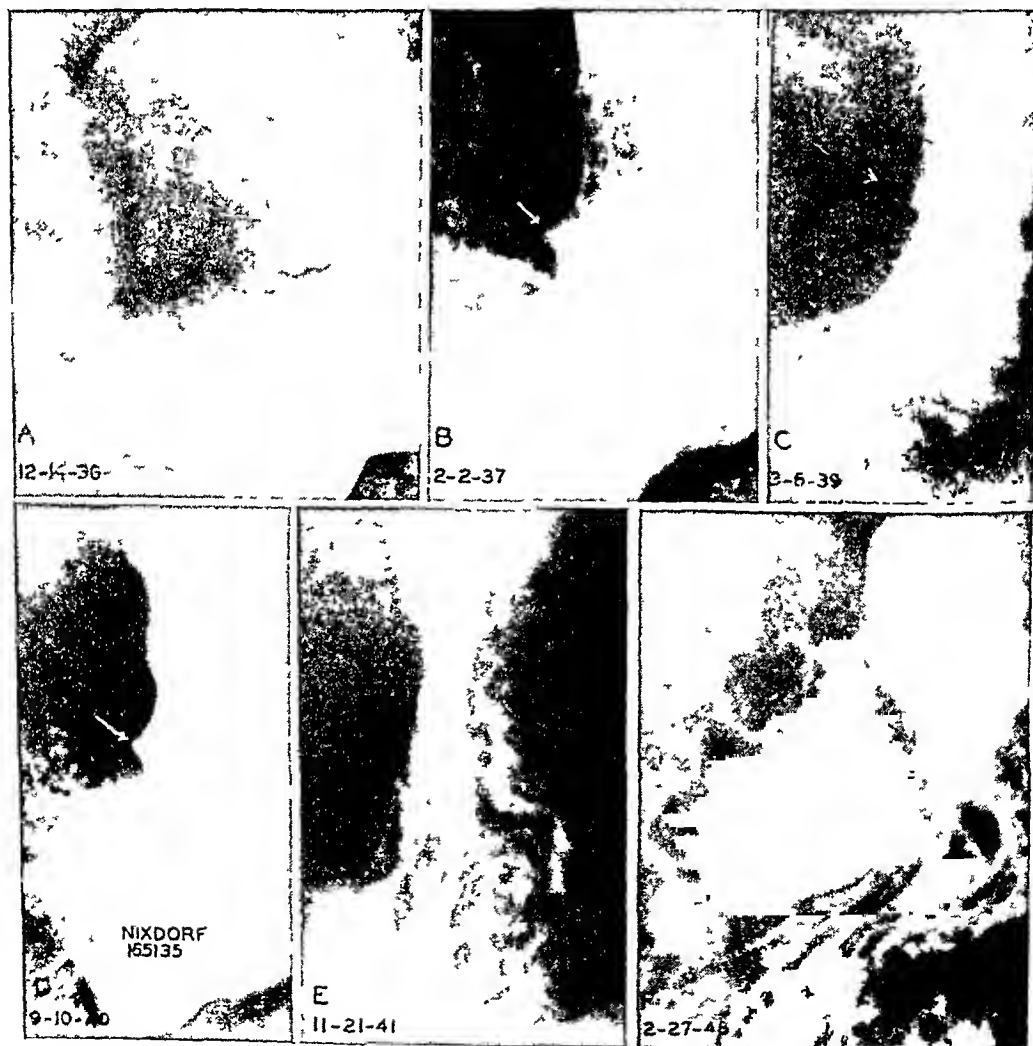


FIG. 1. Case 2. Chronic recurrent gastric ulcer, A, B, C, and D. Spontaneous persistent achlorhydria, 1941. No recurrence, E, F.



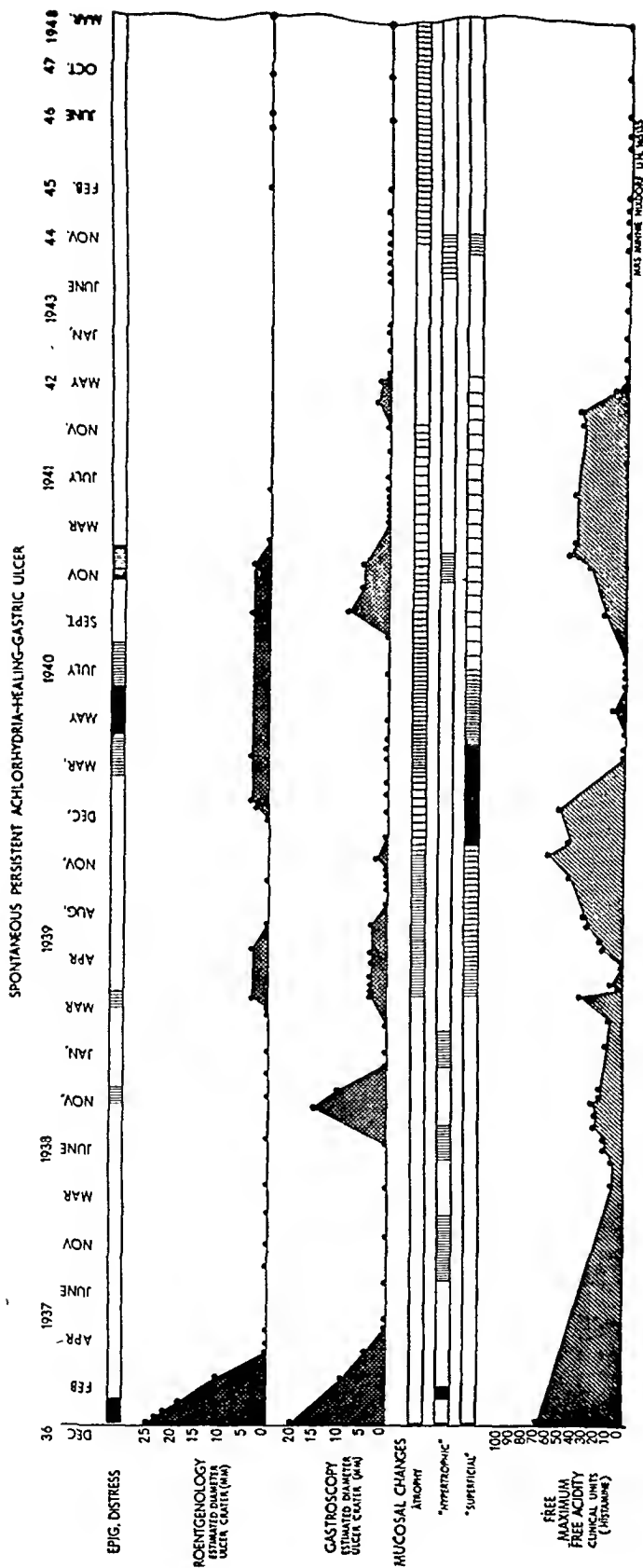


FIG. 2. Case 2. Each dot represents one examination; the vertical lines indicate severity of findings, the greater the distance between lines the less the severity; empty block indicates absence of particular findings.

In 1945 when the patient returned because of osteoarthritic pain, histamine achlorhydria was present and has persisted.

*Case 2* (Figures 1 and 2). M. N., a 63 year old housewife, first developed ulcer distress in 1934. These symptoms subsided after several weeks of treatment with milk and antacids. Severe ulcer pain recurred in 1936, accompanied by protracted nausea and vomiting. When first admitted in December 1936, the maximum free acidity was 75 clinical units. Roentgen and gastroscopic examinations revealed an enormous penetrating ulcer of the lesser curvature of the stomach. The symptoms disappeared completely during 10 days of antacid therapy. In the subsequent 11 years, 26 roentgen examinations and 55 gastroscopies were performed. The patient's course during the first five years was characterized by recurrent distress and reappearance of the ulcer. However, it is noteworthy and significant that in contrast to the original lesion, the recurrent ulcers were always small and transitory (figure 1); the gastric secretion during these years remained low, never reaching the initial level of 75 clinical units. Since 1941 persistent achlorhydria has been found. It thus appears that as the secretory capacity of the stomach decreased the tendency to ulcer formation decreased. In the seven years since the appearance of complete achlorhydria there has been no distress and no roentgenologic or gastroscopic evidence of ulcer.

*Irradiation Achlorhydria.* The history of the effect of roentgen irradiation upon gastric secretion need not be reviewed at this time; it has been analyzed elsewhere.<sup>16</sup> Since the observations reported in 1938,<sup>17</sup> we have studied several hundred patients with various purposes in mind, one of them being to note the effect of achlorhydria upon peptic ulcer. The incidence of prolonged achlorhydria following roentgen irradiation is quite low, just how low we are unable to state at present because of the varying technics used and the incompleteness of the data. However, we do have adequate information on 139 patients in whom achlorhydria developed; complete healing of the ulcer occurred in 134 of these. In the 44 patients with achlorhydria lasting longer than 90 days, complete healing occurred in all (table 3).

TABLE III  
Healing of Ulcer in Post Irradiation Achlorhydria

	Length of Achlorhydria								
	Less than 30 Days			30 to 90 Days			Longer than 90 Days		
	No. Cases	No. Cases Healed	Per Cent	No. Cases	No. Cases Healed	Per Cent	No. Cases	No. Cases Healed	Per Cent
Gastric ulcer	9	9	100	6	4	66	15	15	100
Duodenal ulcer	40	37	92	33	33	100	29	29	100
Jejunal ulcer	2	2	100	5	5	100	—	—	—
Total	51	48	94	44	42	95	44	44	100

*Gastric Ulcer.* Of the 30 patients with gastric ulcer in whom prolonged achlorhydria was produced, complete healing occurred in all but two; in these two the achlorhydria lasted only two months and two and one-half

months respectively. Some of the more dramatic and instructive cases of gastric ulcer follow:

*Case 3* (Figures 3 and 4). N. B., a 40 year old white painter, first seen in April 1942 for distress of six months' duration, gave a history of recurring attacks of epigastric pain of the ulcer type since 1939. A histamine test (0.01 mg. per kg. body weight) disclosed no free hydrochloric acid. A second histamine test several months later revealed a maximum free acidity of 28 clinical units. A roentgen examination of April 11, 1942, revealed an ulcer situated high on the lesser curvature measuring approximately 22 mm. in diameter and 10 mm. in depth. A gastroscopic examination on April 22, 1942 demonstrated the ulcer. Therapy consisted of ambulatory medical management with milk and cream and powders every hour during the day and atropine 1 mg. at night. With this program the symptoms disappeared for several weeks. The ulcer decreased in size. During the next year the free acidity remained low; occasionally no free acidity was recorded. The ulceration was reported to be healed by roentgen-ray in April 1944. However, it recurred in October of the same year, increased in size and in May 1945 measured 20 mm. in diameter. The patient was admitted to the hospital in May, 1945. Three of four histamine tests failed to yield any free hydrochloric acid; one gave a free acidity of 48 clinical units. Radiation

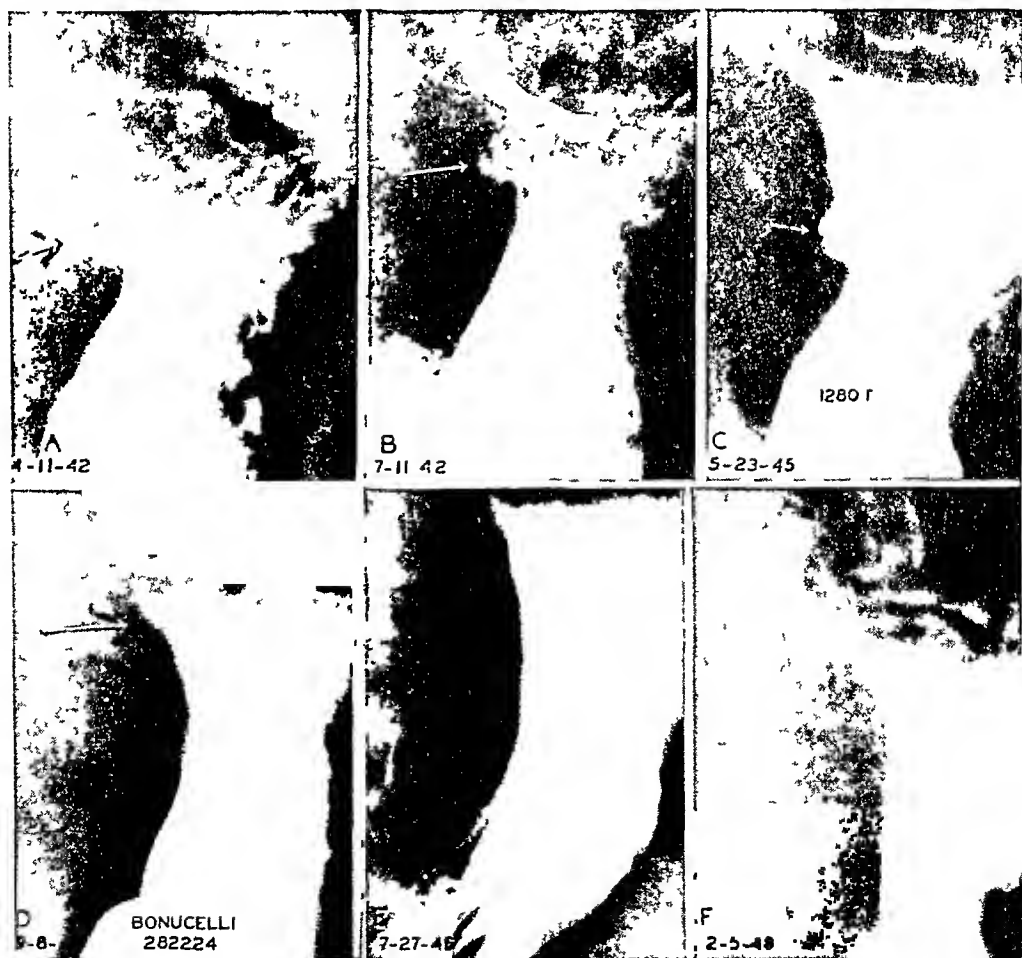


FIG. 3. *Case 3.* Chronic recurrent gastric ulcer, A, B, C, and D. Post irradiation achlorhydria 1945. No recurrence, E, F.

therapy was administered to the fundus of the stomach (total depth dose 1,280 r in 15 days). The response was dramatic; the pain disappeared; the gastroscopic and roentgen examinations revealed a complete disappearance of the ulcer. During the subsequent 32 months the patient has remained well; repeated histamine tests have not elicited hydrochloric acid and the gastric ulcer has not recurred.

*Case 4* (Figures 5 and 6). N. O., a 41 year old male iron-worker of Norwegian descent, in 1938 developed epigastric pain from two to four in the afternoon partially relieved by eating. The pain recurred periodically, lasting for several weeks. A diagnosis of gastric ulcer was made in 1941; ulcer management was prescribed with relief from symptoms for six months but the pain recurred. When first seen, in

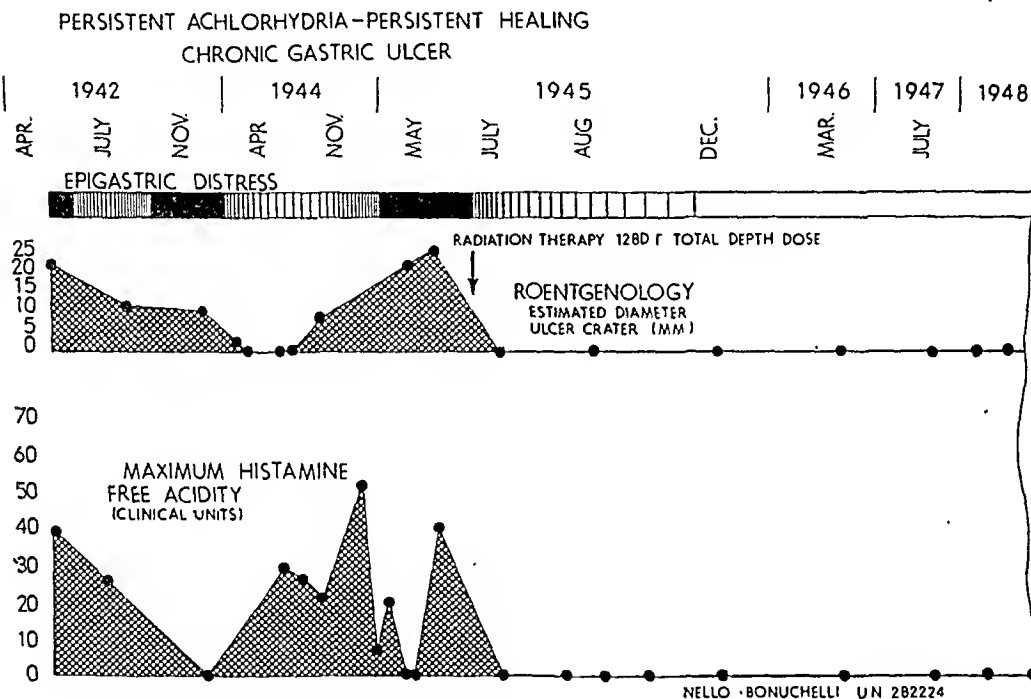


FIG. 4. *Case 3*. Each dot represents one examination.

January 1943, a maximum free acidity (histamine) of 25 clinical units was found. Roentgen-ray disclosed an ulcer 15 mm. in diameter, on the mid portion of the posterior wall of the stomach confirmed by gastroscopy. Ambulatory ulcer management with cream, milk, and powders afford only partial relief. After hospitalization on March 3, 1943 the maximum free acidity (histamine) was 21 clinical units. From March 19 to March 30, 1943 a course of radiation therapy was given with a depth dose of 1,560 r. Progressive decrease in the size of the ulcer was noted by gastroscopy and roentgen-ray; six weeks after completion of the therapy, the ulcer had disappeared completely. On May 19, 1943 no free acidity was obtained after histamine stimulation, nor in repeated tests up to the present time. There has been no recurrence of symptoms or of the ulcer as determined by repeated roentgen-ray and gastroscopic examinations.

*Duodenal Ulcer.* In 102 patients with duodenal ulcer, complete healing occurred in all but three; in these the achlorhydria lasted less than one month (table 3).

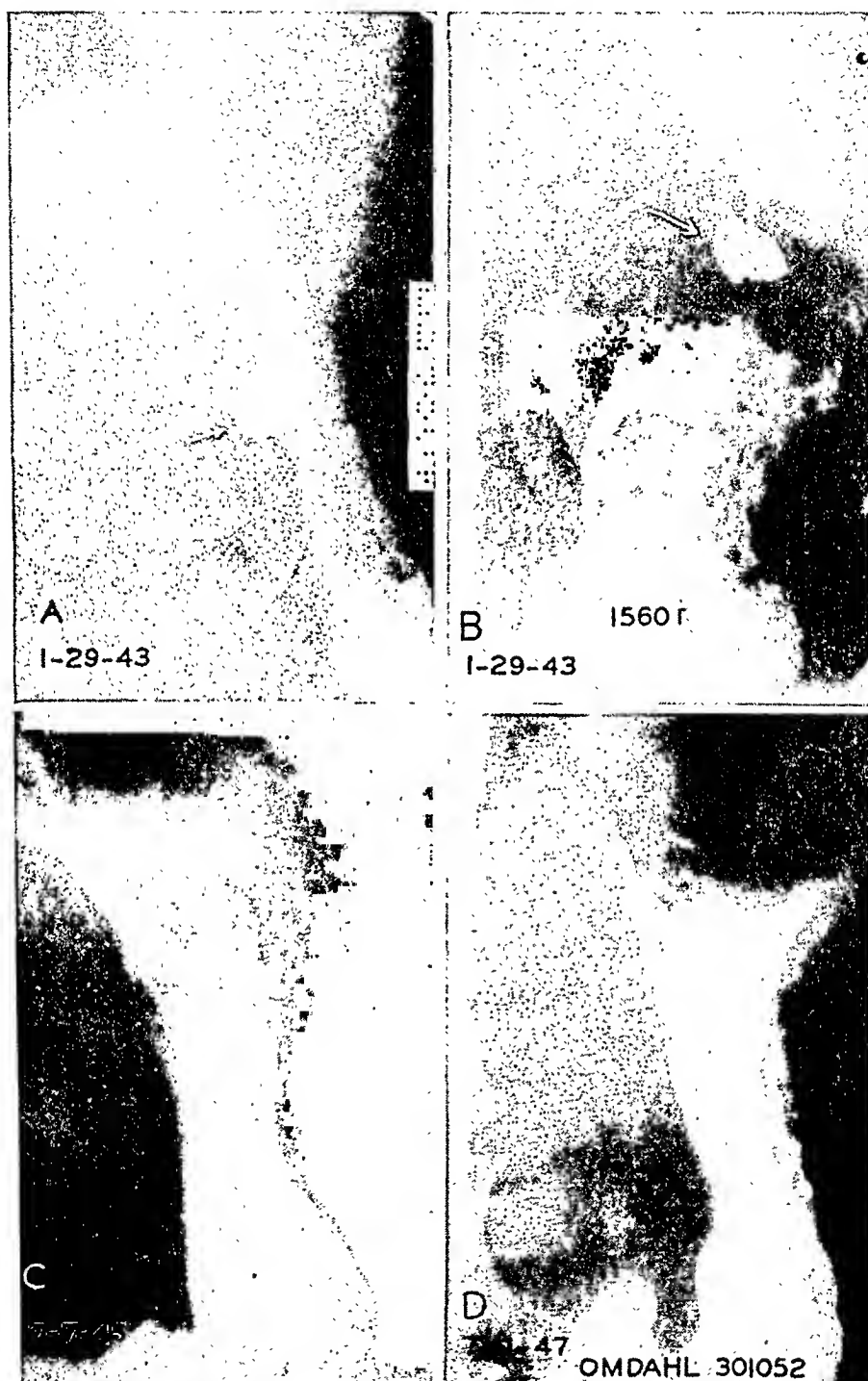


FIG. 5. Case 4. Large gastric ulcer, views A and B, healing three weeks after irradiation. No recurrence to date, views C, D.

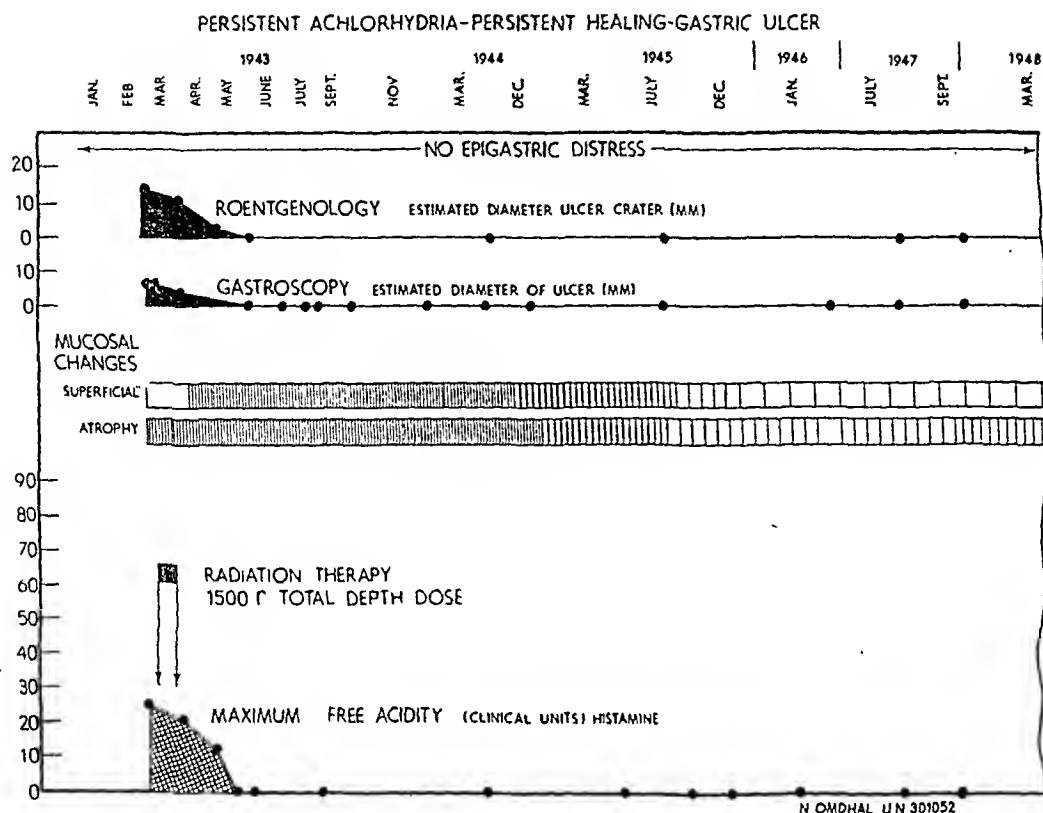


FIG. 6. Case 4. Each dot represents one examination; the vertical lines indicate severity of findings, the greater the distance between lines the less the severity; empty block indicates absence of particular findings.

*Case 5* (Figures 7 and 8). J. E. C., a 41 year old male clerk, first seen in 1944, had had typical periodic ulcer pain for seven years. In 1937 a roentgen-ray diagnosis of peptic ulcer had been made; ambulatory ulcer management had been given with relief but with numerous recurrences lasting one to several weeks. In 1944 roentgen-ray disclosed an active duodenal and a gastric ulcer, the presence of the gastric ulcer being confirmed by gastroscopy. The histamine free acidity reached a peak of 85 clinical units. Hospitalization and strict ulcer management with hourly administration of cream and milk, calcium carbonate 4 gm. every hour, atropine 1 mg. at night and nightly gastric aspirations gave incomplete relief from the severe continuous pain. Radiation therapy was instituted from December 22, 1944 to January 3, 1945, the depth dose being 1,600 r. The pain disappeared completely. The maximum acidity four days after completion of the therapy was only 35 clinical units; two weeks later no free acidity was found. Roentgen-ray showed complete healing of the gastric ulcer in the second week of February, gastroscopically the ulcer was still present 1 to 2 mm. in diameter on March 14, 1945; it had disappeared completely on April 4, 1945. There has been no recurrence of pain, ulcer or acid in the intervening three years.

*Case 6* (Figure 9). J. S., a male office worker, at the age of 35 in 1932 began having periodic epigastric distress lasting for several weeks. In March 1944, he noticed tarry stools. When he was first seen on April 10, 1944, a histamine test disclosed a maximum free acidity of 100 clinical units. A stenosing duodenal deformity with a 4 mm. crater was found by roentgen-ray on April 12, 1944. Radiation therapy, depth dose 1,710 r, was delivered to the fundus and corpus of the stomach from May 4 to May 16, 1944. Achlorhydria developed promptly; the ulcer was reported by roentgen-ray as healed a month after the completion of the radiation. The

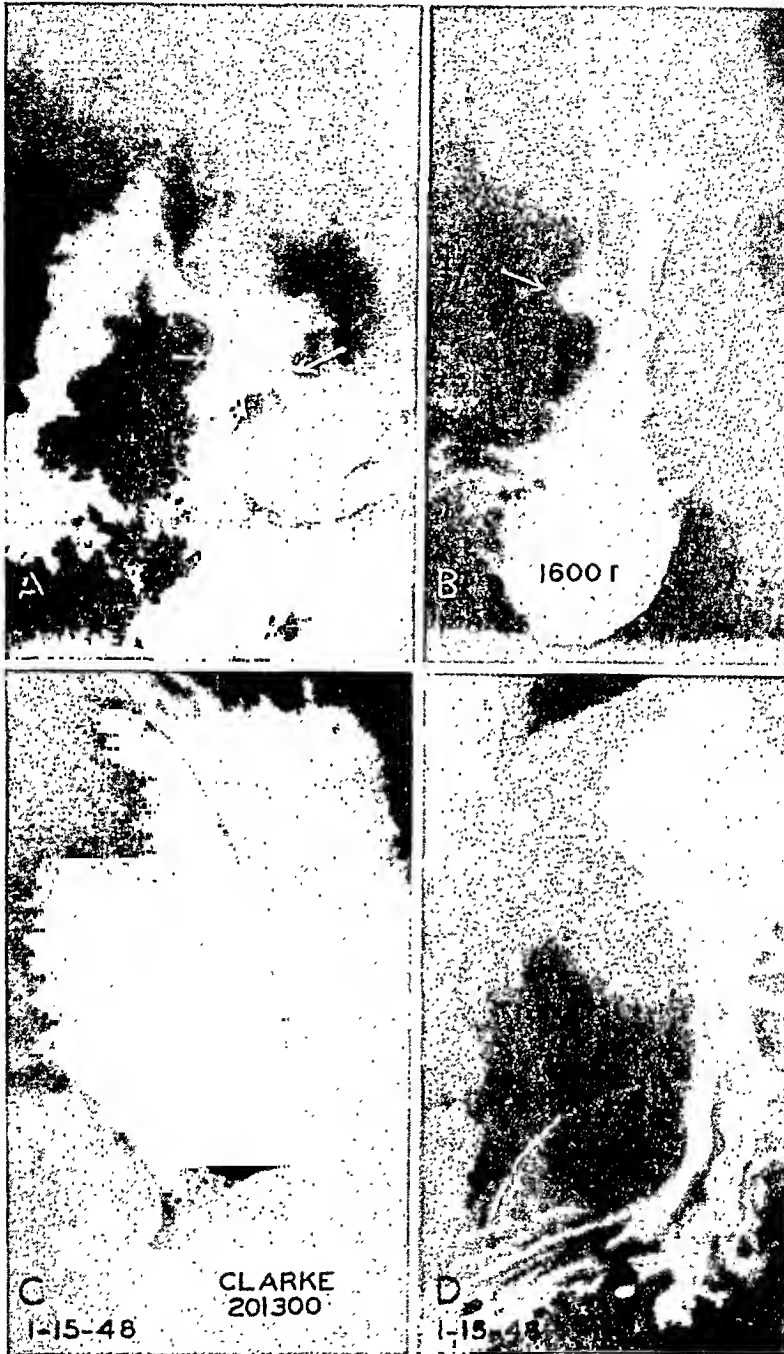


FIG. 7. Case 5. Gastric and duodenal ulcers (definite craters seen by roentgen-ray) in January 1945, healing in six weeks after irradiation, no recurrence to date.

patient was entirely relieved of symptoms and has remained so until the present. Since radiation, repeated histamine tests have disclosed achlorhydria each time; roentgen-ray examinations have revealed deformity but no recurrence of the crater.

*Delayed Radiation Achlorhydria.* In two cases the initial depression of gastric secretion, was not as great as that which occurred later—apparently a delayed reaction due to atrophy of the mucosa resulting from radiation

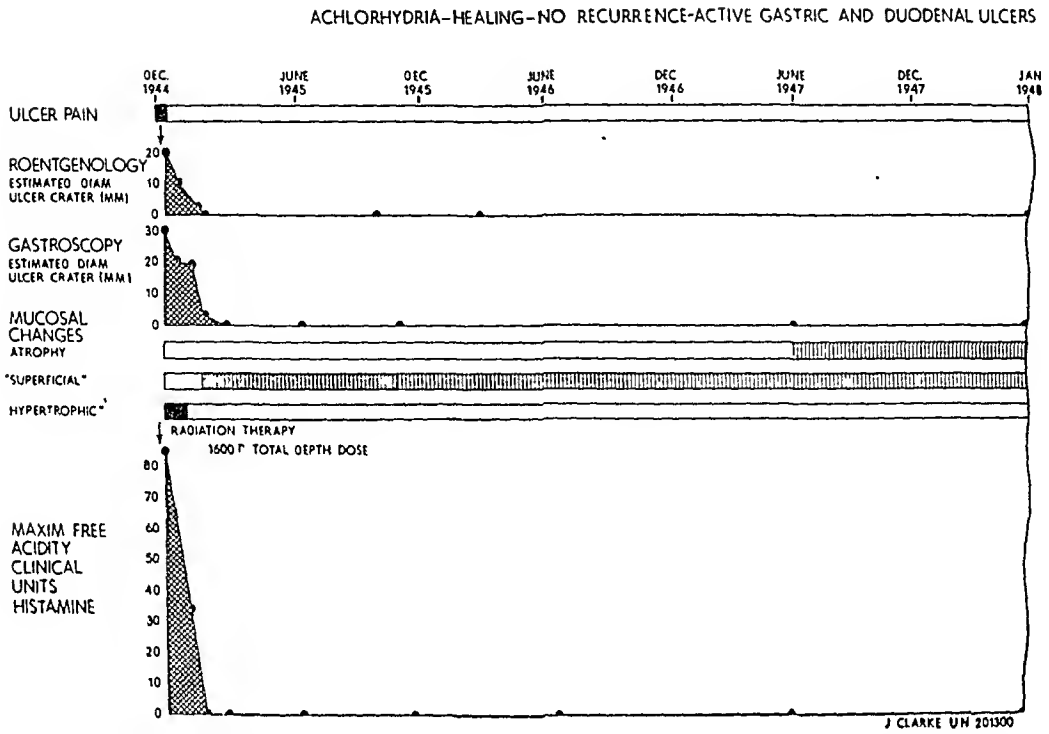


FIG. 8. Case 5. Each dot represents one examination; the vertical lines indicate severity of findings, the greater the distance between lines the less the severity; empty block indicates absence of particular findings.

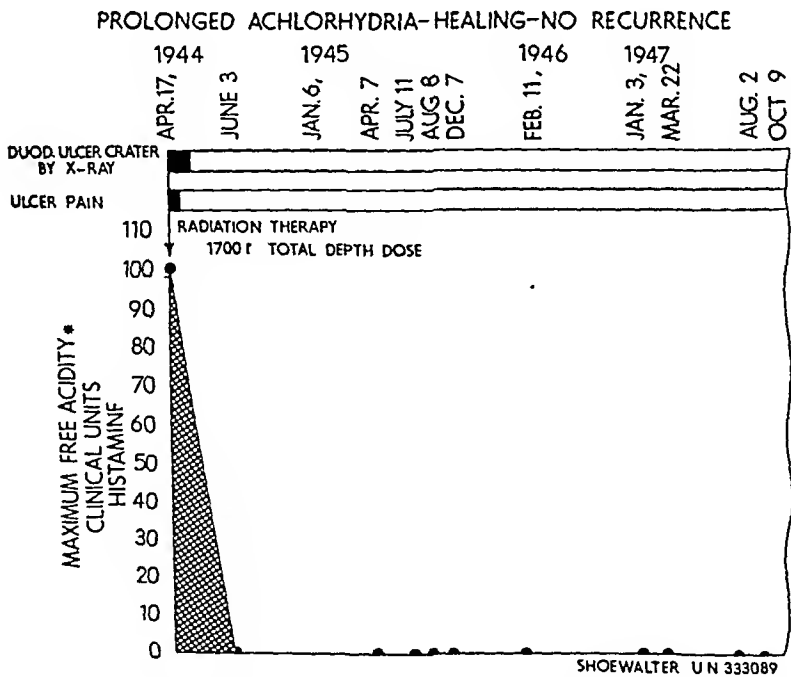


FIG. 9. Case 6. Each dot represents one histamine stimulation.



GASTRIC ULCER

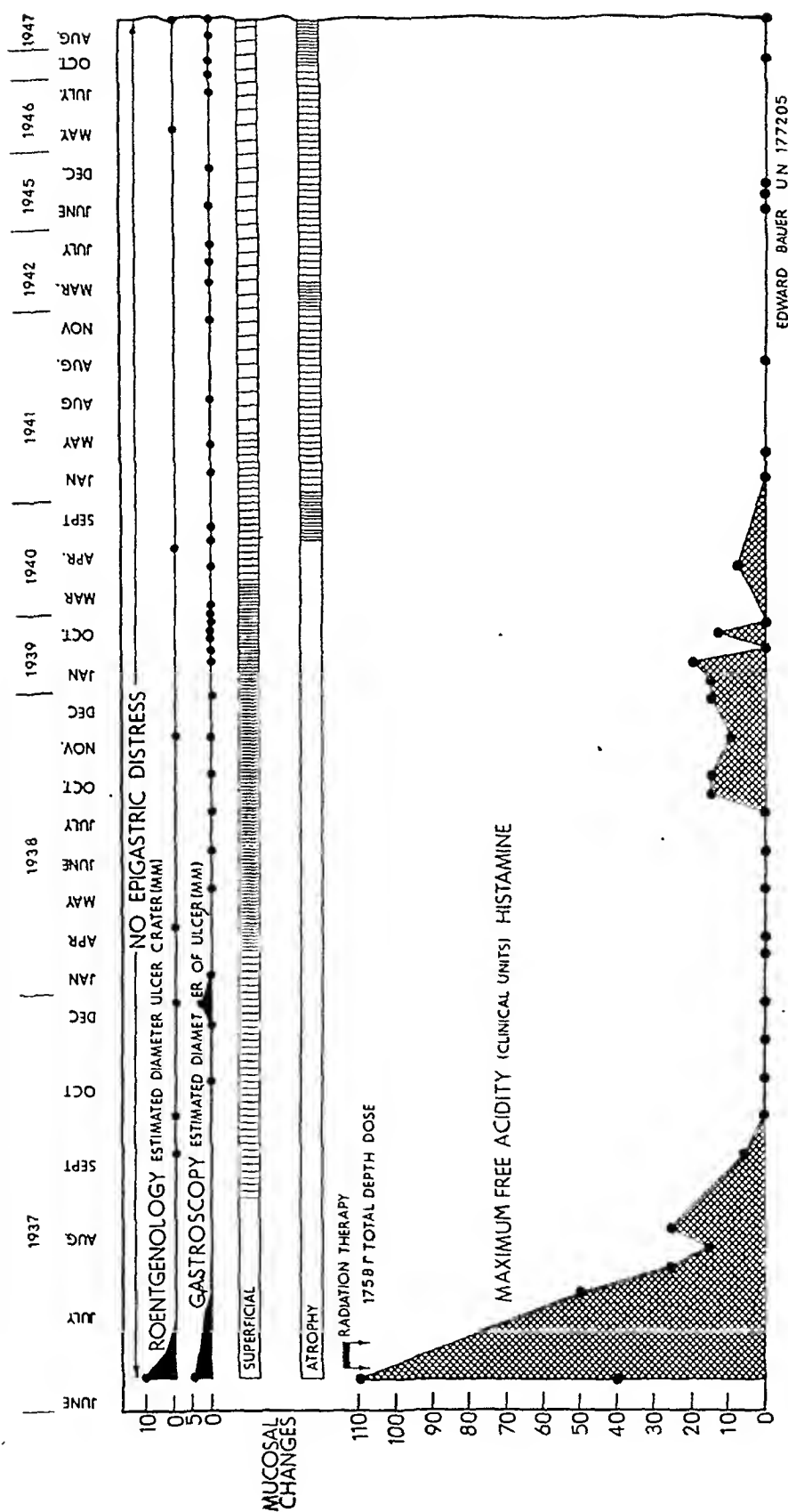


Fig. 10. Case 7. Each dot represents one histamine stimulation.

injury.<sup>18</sup> Healing of the ulcer in these two cases was somewhat slower but it occurred in both when complete achlorhydria developed.

*Case 7* (Figure 10). E. B., a white male, began having ulcer pain and vomiting in 1930 at the age of 43. The pain lasted from a few days to a week and disappeared entirely after a few months. In January 1937, the pain recurred almost daily, was usually present from two to three hours after meals and was relieved only by the intake of food. He vomited frequently, had a poor appetite, and lost nearly 25 pounds in weight. On admission in June 1937, the gastric acidity after histamine reached a peak of 110 clinical units. On roentgen-ray examination a penetrating ulcer about 1 cm. in diameter was found on the lesser curvature of the stomach near the antrum, confirmed by gastroscopy. On medical management including radiation therapy, approximately 1,758 r, the pain disappeared completely. There was a marked and progressive drop in the acidity until October 8, 1937 when achlorhydria developed. Gastroscopy on October 15, 1937, revealed a disappearance of the ulcer. On December 3, 1937, during the achlorhydria gastroscopy disclosed at the angulus a sharply defined shallow, elliptical, yellowish-gray superficial ulcer; on January 5, 1938 this ulcer had disappeared. No free acidity was recorded at repeated histamine stimulations until September 19, 1938, a peak of 15 clinical units being found. A low free acidity ranging from 0 to 21 units was noted until January 28, 1939, when achlorhydria was again recorded. The patient has had no ulcer distress, no free hydrochloric acid, and no return of the ulcer as judged by numerous roentgenologic and gastroscopic examinations since January 1939.

*Case 8* (Figure 11). S. B., a 50 year old white male, began having ulcer pain in 1926 relieved temporarily by a soft diet, but in the following 10 years there were several recurrences. When he was first seen in July 1936 an Ewald test yielded 31 clinical units of free acid. Roentgen examination revealed a large gastric ulcer and a deformity of the duodenal bulb. Gastroscopic examination disclosed a large gastric ulcer. Therapy consisted of a modified Sippy management. The patient improved;

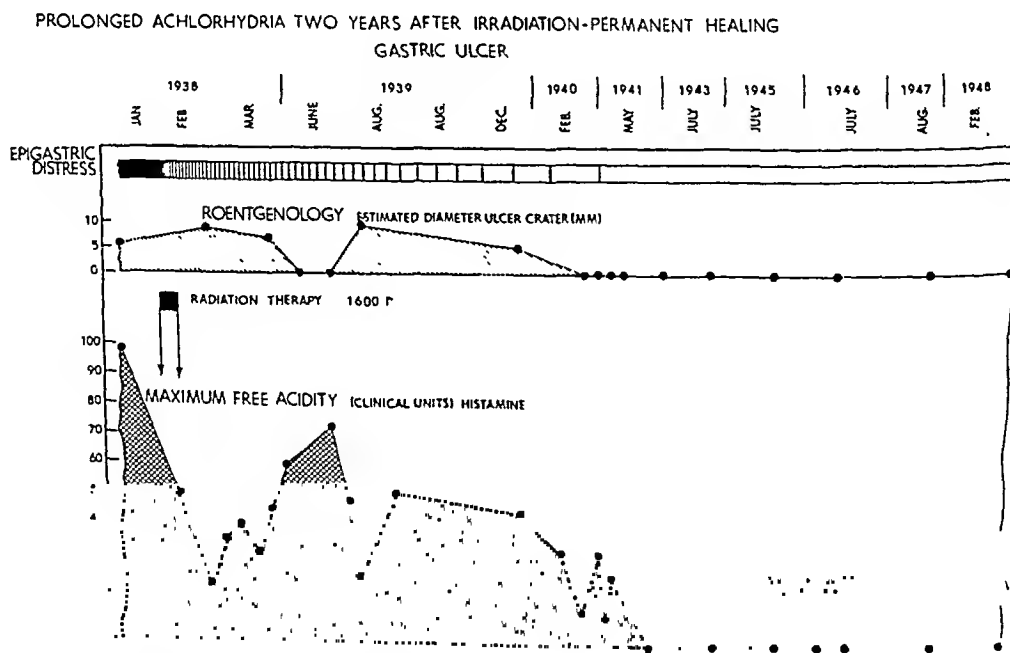


FIG. 11. Case 8. Each dot represents one histamine stimulation.

the ulcer diminished in size and in September was no longer demonstrable. During 1937 there were no symptoms, but very small erosions were demonstrated by gastroscopy in May. In October 1937 a definite ulcer was again seen gastroscopically. A histamine test revealed a maximum free acidity of 100 clinical units. A course of radiation therapy directed at the fundus of the stomach was given, 1,600 r depth dose in 13 days from January 12 to January 24, 1938. The free acidity decreased to 20 clinical units and remained low for a short time; two months later 60 clinical units were found. The ulceration healed in June 1939 but recurred in July and persisted for the following one and one half years. In March 1940, although no additional roentgen therapy was administered, achlorhydria was recorded after repeated histamine stimulation. The ulcer visualized by gastroscopy and roentgen-ray until March 1940, healed and the patient was free from distress. From 1940 to the present time the patient has had no recurrence of pain, of acid, or of the ulcer as judged by repeated gastroscopic and roentgenologic examinations.

*Jejunal Ulcer.* Very few jejunal ulcers were included in the series; the dosage of irradiation was small and prolonged achlorhydria was not obtained.

*Recurrent Peptic Ulcer.* Recurrent chronic gastric, duodenal or jejunal ulcer has not been observed during persistent achlorhydria whether spontaneous or induced, either by surgery or by roentgen irradiation.

## DISCUSSION

The term "peptic ulcer" presupposes the presence of hydrochloric acid for peptic activity occurs only in the acid range of pH, the optimum point being 2.6<sup>19</sup> with activity decreasing to a pH of five. The "peptic" origin of peptic ulcer has received strong experimental and clinical support in recent years. This paper has dealt with two phases of the problem; the occurrence of chronic ulcer in stomachs possessing a low secretory ability and the effect of complete prolonged achlorhydria on the course of peptic ulcer. Chronic gastric ulcer does occur in patients with transitory achlorhydria and in patients with low secretory ability, but not in complete and permanent achlorhydria. Low acid secretions were noted in 21 per cent of the gastric ulcers studied in this series, but not in a single instance of active duodenal ulcer. Thus peptic ulcer may occur without "hyperacidity" or "hypersecretion" but not with persistent "anacidity."

Further evidence of the validity of the concept of "peptic" ulcer is provided by the invariable healing observed following the appearance of achlorhydria (spontaneous or induced) lasting 90 days or longer, by the very high incidence of healing in phases of achlorhydria of less than 90 days' duration, and by the failure of the ulcer to recur during the period of achlorhydria. It seems evident that if there were a simple means of producing permanent achlorhydria the ulcer problem would be solved. There may be, and doubtless are, other solutions; perhaps a 50 per cent reduction in the gastric secretory rate would be sufficient to produce permanent cures.

The question of why the stomach does not digest itself, asked by John Hunter<sup>20</sup> in 1778, is still unanswered, although much is known about it. The protection afforded the mucosa by the constantly secreted layer of mucus

has been recognized for many years<sup>21, 22</sup> as has the varying susceptibility of the stomach, duodenum and jejunum to peptic digestion. The purpose of this paper has been to focus attention upon the basic problem of "peptic" ulcer by demonstrating the invariable presence of acid gastric content and likewise the invariable healing effect of prolonged achlorhydria.

### CONCLUSIONS

1. Chronic peptic ulcer occurs only in association with acid gastric secretion.

2. Achlorhydria lasting longer than three months produces complete healing of peptic ulcer irrespective of the age of the patient or the duration of the disease.

3. Spontaneous or induced achlorhydria, if permanent, produces permanent healing of peptic ulcer.

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# PROBLEMS IN THE NATURAL HISTORY OF POLIOMYELITIS \*

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THE people who have worked for many years gathering information on the natural history of poliomyelitis are more impressed with the tremendous amount that remains to be learned than with what is known at the present time. That is not to say that in the approximately 40 years since the discovery of the virus etiology of the disease, there has not been accumulated a great deal of basic information, but what we know is still so sketchy that different investigators can interpret the available data in different ways. In this discussion I shall deal especially with the events which follow human infection with poliomyelitis virus and its mode of spread.

It is no longer mere epidemiologic hypothesis to regard paralytic poliomyelitis as only one part of the clinical spectrum which results from infection with poliomyelitis virus. Although there are as yet no simple tests for poliomyelitis infection in the individual case, the data very laboriously collected thus far suggest that following introduction and multiplication of the virus in the human body the following events may ensue: (1) no obvious signs of disease, (2) a febrile illness of one to seven days' duration associated with any one or all of the following symptoms—headache, mild sore throat, nausea, vomiting, abdominal pain, (3) the preceding syndrome plus distinct nuchal or spinal rigidity, and (4) the preceding syndrome with varying degrees of paralysis and other signs indicative of involvement of the central nervous system.

Let us now examine the extent of our knowledge on the behavior of poliomyelitis virus in the human body which would explain this clinical spectrum and also provide a basis for our evaluation of the various potential modes of spread. Our information for this kind of synthesis must be derived chiefly from studies on human beings—during life as well as post mortem—although it is obvious that the answer to certain questions on pathogenesis can come only from judiciously designed animal experiments. The few observations which were available on human beings only 10 years ago and the injudicious deductions from animal experiments led to a concept of human infection which limited the field of operations for the virus to the olfactory mucosa and certain parts of the central nervous system. This concept was given up, as is well known by now, because both virus assay<sup>1, 2</sup> and pathological studies<sup>3, 4, 5</sup> on fatal spinal and bulbar paralytic cases showed that the

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pattern in human beings did not correspond to that found in monkeys<sup>6</sup> and chimpanzees<sup>7</sup> infected with poliomyelitis virus by the olfactory pathway. Although analogies are sometimes very helpful for orientation they also have their limitations. Certain phenomena in poliomyelitis, such as the well-established excretion of the virus in the stools, have been compared with pulmonary tuberculosis, scarlet fever, etc. where the etiological agent may be similarly excreted without it constituting a significant factor in the transmission of the disease. We must ask ourselves then whether or not poliomyelitis is in other respects also like pulmonary tuberculosis or scarlet fever or measles? Does the poliomyelitis virus multiply in or reach the lungs, the trachea, the nasal mucosa in any significant amounts?

It should be pointed out here that the death of the "olfactory pathway" concept of poliomyelitis has not eliminated from consideration the respiratory tract as the chief extraneural system involved in poliomyelitis, as reference to the most recent epidemiological literature will make clear.<sup>8, 9, 10, 11</sup> What, then, are the facts with regard to the peripheral sites in which poliomyelitis virus is demonstrable with regularity in human beings—dead or alive? Since much of the controversy or indecision centers around the respiratory tract versus the alimentary tract it may be well to draw the line between them anatomically, particularly where they cross each other in the oropharynx. For this reason one must consider separately results obtained with nasal secretions and nasal mucosa from those with so-called "nasopharyngeal secretions or washings" in which material from the oropharynx is obviously included. Results which are regularly obtained only with material from the oropharynx and *not* with that derived from the nose or lower respiratory tract seem to me to belong more appropriately in considerations of the alimentary tract. Prior to 1941, there were only scattered reports in the literature of tests on this or that tissue from fatal cases of poliomyelitis, and in the earlier days care was not always taken to avoid contamination.<sup>12</sup> A systematic study of the topography of the virus throughout the body of seven patients, who for the most part died within a few days after onset of symptoms, was reported in 1941<sup>1</sup> and a still more extensive study of the localization of the virus in various levels of the alimentary tract was carried out subsequently on six additional fatal cases.<sup>13</sup> As is well known by now, these studies established the fact that the washed tissues of the alimentary tract were the only sites in which the virus was *regularly* found outside of the central nervous system. When multiple levels were tested the virus could be found somewhere in the tissues of the alimentary tract in each patient. In any given case the virus was detected only in the pharynx or only at some level of the intestinal tract or in both, and this without reference to whether the primary paralysis was bulbar or spinal. It cannot be stressed too often that in no instance in these studies was virus found in the nasal mucosa. In the entire literature on poliomyelitis there is only a single report made by Flexner and Amoss<sup>14</sup> in 1919 in which the virus was said to have been re-

covered from the nasal mucosa of one of three fatal cases tested. In view of Flexner's statement<sup>12</sup> in 1936 that in the earlier years admixture with positive tissues could not be ruled out, and since it is also possible that during the terminal state there may be contamination of the nasal mucosa with material from the oropharynx, it is difficult to assign too much weight to this single finding, particularly since tests in later years on washed tissue removed with special care to avoid contamination yielded only negative results. It is also noteworthy that in no instance was virus recovered from the salivary glands or the urinary bladder of human cases, in whom poliomyelitis virus was readily demonstrated elsewhere in the body. Nor with all the possibilities for aspiration, has the virus been demonstrated unequivocally in the trachea or lungs.<sup>1, 13</sup> The pattern of virus distribution in a series of cases is more important than any isolated positive finding, and the almost regular or constant absence of virus in certain parts of the body cannot be dismissed from consideration on the grounds that negative findings are of no significance, when the same methods and procedures have served to demonstrate the almost regular presence of the virus in other peripheral tissues of the same individuals.

Nevertheless, it is known from studies on the pathogenesis of other neurotropic virus infections in experimental animals, that the pattern of virus distribution may be quite different early after invasion and before involvement of the central nervous system, from that which may be found at death. It is important to examine, therefore, what is known about the presence of poliomyelitis virus in the human body during life and particularly during the earliest stages of the infection. As regards the blood the early reports were all negative, and more recent work<sup>15</sup> with concentrated, ultracentrifuged preparations from 111 patients, most of them bled within a few days after onset of symptoms and 20 within less than 24 hours, yielded a positive result in a single abortive or nonparalytic patient. No virus has been found in the urine.<sup>2, 16</sup> The nasal secretions alone, as distinguished from combined nasal and pharyngeal washings commonly referred to as "nasopharyngeal secretions," have been studied on two occasions in 41 patients and have not yielded a single unequivocal positive result. In one of these studies on 22 paralytic patients<sup>16</sup> the pooled secretions collected on multiple cotton plugs inserted deep in the nasal cavities over a period of three consecutive days, failed to yield virus even when the collections were started within three days after onset of first symptoms. Similar negative results were obtained with the saliva and oral secretions expectorated naturally without hawking or coughing over a period of three days by 20 paralytic patients. However, single specimens of stools or enemas obtained at the termination of each three-day period yielded virus in 10 of these patients.

In the second study<sup>17</sup> on 19 patients, all within four days after onset of symptoms, the throat and nose were swabbed separately after, however, the



patients had been induced to talk, blow, cough and expectorate for one-half hour into sterile gauze masks which were tied over the patient's mouth and nose. The throat swabs yielded virus in six of these patients, the nose swabs in one, and the wet portions of the masks in two. Since the same patient who yielded the positive nose swabs also had virus in the mask and since the nose was swabbed after the mask had been contaminated, the authors<sup>17</sup> are not willing to interpret this result as an unequivocal demonstration that virus is present in the nose under normal conditions. The report of Kessel and his associates<sup>2</sup> that only negative results were obtained in tests on nasal washings from 139 patients is of interest in this connection, especially since it is not clear that they may not have dealt with nasopharyngeal rather than nasal washings. The repeated demonstration of virus in the tissues of the oropharynx and in washings from this region<sup>18, 19, 20, 21</sup> particularly during the early stages after infection, can hardly be used as evidence for involvement of the respiratory tract in poliomyelitis. The oropharynx is properly part of the alimentary tract and the intriguing point in the available observations lies rather in the fact that virus is only infrequently recovered from this region after the first week, while the stools continue to be infective for many weeks.<sup>22</sup> In this respect Dr. Thomas Francis has often recalled in recent years the almost forgotten reports<sup>23, 24</sup> that typhoid bacilli could be recovered from the throat and mouth of approximately 50 per cent of patients with typhoid fever. Since the work of Hamburger and his associates<sup>25</sup> has shown how limited is the escape to the exterior of streptococci and presumably other infectious agents which are present only in the throat, and that the "nasal carriers" are the "dangerous carriers" from the point of view of dissemination, it would appear to be of the greatest importance to establish as unequivocally as possible by further studies on patients in the earliest stages after infection the extent to which the nasal mucosa and the oral secretions under ordinary, not artificial circumstances, may be a source of poliomyelitis virus. If the present negative results are confirmed, it should have a bearing not only on epidemiological thinking but also on public health practice.

For the present, however, our chief concern in the pathogenesis of the infection is with how the virus which is demonstrable in various levels of the alimentary tract gets there and where it multiplies during the many weeks of its excretion in the stools. The simplest assumption would have it that as virus is swallowed it invades the tissues at one or another or many levels of the alimentary tract and multiplies locally. That poliomyelitis virus can pass through the secretions of the stomach and intestines unharmed has been shown many years ago, but when it failed to multiply as with certain strains in rhesus monkeys, it could not be detected in the stools for more than two to three days after feeding.<sup>26</sup> There are, however, certain difficulties connected with the hypothesis of local multiplication. There is at the present time no evidence that the virus can multiply in any cells other than nerve cells, and because of the extreme host and tissue specificities of the polio-

myelitis viruses it would be most difficult to devise an experiment with an appropriate strain of virus that could answer this question unequivocally. Certain it is, however, that the mere capacity for even extensive multiplication in nerve cells is not sufficient to insure multiplication in the alimentary tract. Some of the strains of virus that are most highly virulent for either the rhesus, cynomolgus or African green monkeys, among them the well known M. V. strain and the Brunhilde strain of Howe and Bodian, pass through the alimentary tract of these animals without either local multiplication or production of the disease.<sup>27, 28</sup> Certain other strains of recent human origin, however, such as the "Per," produced the disease quite readily after being fed in the form of cynomolgus nervous tissue to cynomolgus monkeys and could be detected with great ease throughout the entire alimentary tract—washed tissues as well as contents—at the onset of paralysis.<sup>13</sup> Similar results were obtained by Faber<sup>29</sup> with this strain of virus, but after only a few additional passages in rhesus monkeys Howe<sup>30</sup> was unable to infect any of a large number of cynomolgus monkeys with this strain.\* The successful infection of chimpanzees by the oral route with human stools<sup>31</sup> as well as with a variety of monkey-adapted<sup>32</sup> and also mouse-adapted poliomyelitis viruses<sup>33</sup> is now well established, as is the fact that chimpanzees like human beings can then excrete the virus in their stools for as long as two months.<sup>32</sup> It is clear, therefore, that a poliomyelitis virus must possess some property in addition to its neurocytotropism as measured by its virulence for the central nervous system, in order to be able to multiply in or invade from the alimentary tract. Thus while the submucous and myenteric plexuses of nerve cells, which are so abundantly distributed in the alimentary tract, might be considered as the sites for virus multiplication, it is not clear why they are not attacked by all virulent strains. Although it is conceivable that virus multiplication could occur without necessarily destroying these nerve cells, it would have to continue over a much longer period than is ordinarily the case in the central nervous system.

Faber and Silverberg<sup>34</sup> recently postulated that "almost any nerve system with peripheral endings in the mucous surfaces *can*, if exposed, convey virus in a central direction to its regional ganglia" and that "the primary lesion of poliomyelitis occurs in the peripheral ganglia." According to this view there is no local multiplication at all at the portal of entry, and the presence of virus in the peripheral tissues would be due to a retrograde centrifugal axonal spread from the first neuronal cell bodies affected by the virus. In my opinion, the greatest difficulty in the way of this attractive hypothesis is the fact that highly virulent strains of poliomyelitis virus cannot invade the central nervous system of rhesus monkeys from either the nasal, pharyngeal or intestinal mucosas when the olfactory tracts are cut, and even more recently

\* Since the presentation of this paper, Howe and Bodian (Am. Jr. Hyg., 1948, xlviii, 99-106) reported that while "Per" virus derived from rhesus monkeys failed to infect cynomolgus monkeys by the oral route, that derived from cynomolgus monkeys produced such infection with the same incidence as originally reported by Sabin and Ward.<sup>27</sup>

recovered strains such as Howe and Bodian's "Brunhilde" virus, in spite of possessing an intracerebral titer of  $10^{-5.4}$ , failed to multiply in or penetrate the mucous surfaces of the alimentary tract after being fed to baby African green monkeys.<sup>28</sup> It cannot be said, therefore, that all that is required is a virulent virus and any mucous surface with exposed nerve endings.

The observations of Trask and Paul,<sup>35</sup> later extended by Melnick,<sup>36</sup> which showed that in occasional chimpanzees and monkeys inoculated with certain strains of virus intracutaneously, subcutaneously or intraperitoneally (but as a rule *not* after intracerebral inoculation) virus may subsequently be recovered from the stools, suggested that virus may localize in the alimentary tract without necessarily being swallowed. That such localization is most likely not due to centrifugal spread from the central nervous system is suggested not only by the fact that virus could be found in the stools several days before the appearance of paralysis,<sup>36</sup> but that following the extensive multiplication of virus which occurs after intracerebral inoculation, the virus has never been found in the stools by other investigators<sup>26, 37</sup> and only once in Melnick's<sup>36</sup> tests on 28 monkeys. Although one wishes that these animals in New Haven had not been exercised "in a common runway" where they might have picked up some virus from the feces of other monkeys (such spontaneous infections have now been reported<sup>38</sup>), it is, nevertheless, possible that in occasional parenterally inoculated animals the virus could enter the blood stream<sup>13, 27, 39</sup> and then localize in the alimentary tract. In young mice inoculated intravenously with the virus of St. Louis encephalitis it has been demonstrated that almost simultaneous localization and multiplication occurred in the intestinal tract and brain.<sup>40</sup> It may be noted parenthetically, however, that despite extensive multiplication in the intestines, the St. Louis virus was not excreted in the stools.

As regards the pathways by which the human nervous system is invaded from the periphery, the available bioassay and pathological studies have led Howe and Bodian and myself to agree that they only serve to exclude the olfactory system and the blood stream as possible pathways of the virus and to suggest that the cervical and abdominal sympathetic nerves are infrequently if ever used as pathways for invasion of the central nervous system.<sup>5</sup> The frequency with which the bulbar form of the disease is exhibited by monkeys inoculated into the pharyngeal region<sup>41</sup> and by patients who develop poliomyelitis after tonsillectomy,<sup>42, 43</sup> and the small proportion of the bulbar type among the general run of cases, perhaps suggests that the nerves of the pharynx do not constitute the most frequent pathway. The same objection may perhaps be raised against the vagus nerve, which supplies almost the whole intestinal tract except for the descending colon and rectum, even though there is experimental evidence that primary spinal paralysis may occur in a proportion of animals, in whom viral invasion occurred along the nerves of the throat<sup>41</sup> or the vagus.<sup>44</sup> Since nuchal and spinal rigidity or spasticity are almost invariably found before the appearance of paralysis,

and since Bodian <sup>46</sup> has recently reported that in the preparalytic stage of experimental poliomyelitis, spasticity, tremor and hyper-reflexia of the leg muscles can occur in the absence of virus or lesions in the lumbar spinal cord, but apparently as a result of lesions in the reticular formation and vestibular nuclei of the medulla and the roof nuclei of the cerebellum, it may be that the medulla is the primary site of invasion in the human central nervous system. On the other hand, the not infrequent history of regional cutaneous hyperesthesia, sometimes for several days prior to the development of primary lower spinal paralysis, has suggested that there may be primary involvement of the dorsal root ganglia via the afferent sensory fibers from the gut; the difficulty with this hypothesis is that there is still some question among anatomists as to whether or not there are sensory fibers in the gut with cell bodies in the dorsal root ganglia, and if so whether or not they are limited to the serosa or mesenteric attachment. This, then, is the dilemma and we may ask whether there is any way to resolve it for the human disease, and if not, how much light can be derived from further studies on experimental animals? Faber and Silverberg <sup>34</sup> have recently attempted to supply the answer to some of these questions by a histopathological study of the peripheral cranial and sympathetic ganglia in fatal human cases. Bodian and Howe <sup>44</sup> in a recent communication on the significance of lesions in peripheral ganglia in chimpanzee and human poliomyelitis have challenged the conclusions of these authors on the basis that the lesions in the sympathetic ganglia could not be regarded as specific for poliomyelitis while those in the craniospinal ganglia in fatal cases or even in the earliest paralytic stage in experimental animals cannot serve as indicators of primary portal of entry, since at that stage they are invariably involved by centrifugal spread of virus from the central nervous system. My own observations <sup>13</sup> lead me to agree with Bodian and Howe <sup>44</sup> in their conclusion that it is not possible to obtain the answer to this particular question from a histopathological study of material from fatal human cases. I do believe, however, that it should be possible to obtain the answer by an extensive, judiciously designed virus assay study on cynomolgus monkeys or chimpanzees sacrificed at various stages after feeding of a strain of virus which would produce paralytic poliomyelitis in them.

The last question I would like to take up in our consideration of the events which follow human infection with poliomyelitis virus is concerned with the distribution and effects of the virus in the subclinical, so-called abortive, nonparalytic, and transitory paralytic forms of the disease. In 1941, unequivocal evidence was published indicating that subclinical or nonparalytic forms of poliomyelitis infection not only existed in monkeys inoculated with strains of recent human origin but that they were associated with neuronal lesions of varying extent in the same centers of the central nervous system which are affected by the virus in the paralytic disease.<sup>46, 47</sup> It was furthermore shown that the virus need not necessarily destroy all the

affected neurons but may produce only partial degenerative changes from which recovery is possible.<sup>46, 46a</sup> Since evidence of extensive neuronal destruction could be found in the spinal cord of monkeys exhibiting no evidence of paralysis, it was apparent that the segmental distribution of the lesions could be of such a nature that there would be no interference with the major innervation of a given muscle. Similarly, it was found that the transitory character of paralysis occasionally observed in monkeys was also on the basis of specific effects on the neurons.<sup>46</sup> In human infection the question remained whether in the many subclinical or mild abortive cases without any physical signs pointing to involvement of the nervous system, there, nevertheless, was such involvement, or whether viral multiplication was limited to the peripheral tissues. In 1945, Bodian and Howe<sup>32</sup> reported that among seven chimpanzees with clinically inapparent or nonparalytic poliomyelitis but excreting virus in their stools, there was none without lesions of some kind in the central nervous system. They stated that because of the great similarity in the response of chimpanzees and human beings to infection with poliomyelitis virus, there was reason to believe that in human beings also, the so-called systemic or peripheral type of inapparent poliomyelitis, with virus restricted to peripheral tissues and ganglia, may be rare or nonexistent. In 1946, I had an opportunity to study an outbreak of poliomyelitis among American marines in Tientsin, China, and found that lumbar punctures had been done on at least 40 men who had only a very mild transitory febrile illness without any detectable nuchal or spinal rigidity; in 25 of these, pleocytosis was present ranging from 50 to 500 cells per cu. mm. During the past summer (1947), Dr. A. J. Steigman and I studied a mild illness of which there were many thousands of cases among the children of Cincinnati, Ohio, and which was generally called "summer grippe" or "summer sore throat."<sup>47a</sup> Among 10 such children, who were representative of thousands that were left at home, we found five with pleocytosis, and from two of the remaining five, without either pleocytosis or nuchal-spinal rigidity, we recovered poliomyelitis virus. In poliomyelitis, pleocytosis results from an overflow of cells from the Virchow-Robin spaces, which to begin with were most probably called forth by some neuronal injury.<sup>48</sup> Nor can it be said that the absence of pleocytosis in the other patients necessarily indicates that the central nervous system was not involved.

The factors which determine the limited multiplication or dissemination of poliomyelitis virus within the central nervous system in those with inapparent or nonparalytic infections are little understood and should provide an important field for future study. That one factor is to be found in the host is evident from the fact that from the central nervous system of nonparalytic monkeys which had successfully halted the infection in the spinal cord or prevented its extension to the spinal cord, it was still possible, several weeks after the acute stage, to recover virus which in other monkeys produced the severe paralytic disease.<sup>46</sup> The extent to which such an equi-

librium or "armed truce" between the virus and the host may exist in human beings who exhibit no signs of infection or only a very mild "summer grippe" or "summer sore throat" is unknown, but that it exists is highly probable. The frequency with which fatiguing exercise or severe exertion may be followed by paralysis after an interval of 24 hours or less in individuals with a history of antecedent minor illness or even without any such history, suggests that the virus was probably already in the central nervous system at the time of the physical stress, and that this provocative factor might have upset the equilibrium between the virus and the host achieved at some earlier time.<sup>40, 49, 49a</sup> Although the question of the existence of strains of poliomyelitis virus with inherently low virulence, irrespective of the status of the host, has often been considered, there has been no conclusive experimental work on it. The fact that strains of very high virulence for the monkey have been recovered from very mild or inapparent human infections has emphasized the rôle of the host. However, during the recent Cincinnati epidemic of so-called "summer sore throat" or "summer grippe," we have found evidence suggesting the operation of strains of poliomyelitis virus of very low virulence for monkeys in many of these minor illnesses, while strains of high virulence for monkeys were recovered from paralytic cases which were occurring at the same time.<sup>47a</sup> Also to be considered in this connection is the growing body of evidence which indicates that there is not just one immunological type of poliomyelitis virus but many. It is not improbable that the antigenic complexity of different strains may be such that in some instances infection with one type may confer no immunity at all against another, while in others there may be a partial immunity which could modify the course of subsequent infection.

In the last part of this discussion, I should like to consider some of the issues which contribute to the uncertainty which still surrounds the question of dissemination of the virus in nature, with special reference to how it reaches the person who will become infected. Although the bulk of the evidence continues to point to man as the primary and chief reservoir of the virus, it is not at all settled, as some would have it, that intimate association with other human beings is the chief and most important means of transmission. First of all what is the present status of the existence in nature of hosts other than man? Leaving out of consideration the unusual circumstances in which a chimpanzee or special breed of monkey may become spontaneously infected, is there any evidence that domestic animals or birds or rodents may be hosts for the virus and sources of human infection? In two recent communications, it was reported by one investigator<sup>50</sup> that three of 37 dog serums in Chicago, and by another group of investigators<sup>51</sup> that 78 per cent of 55 domestic cows, 63 per cent of 48 domestic horses, and 44 per cent of 112 domestic chickens, among other animals tested, neutralized the Lansing mouse-adapted virus. There is no question now that the Lansing mouse-adapted virus represents a *bona fide* human poliomyelitis virus,

immunologically identical with a number of other strains of human poliomyelitis virus and yielding similar results in tests with human sera as were obtained with the monkey strains. Is it possible then to conclude from these reports that like the arthropod-borne encephalitis viruses, poliomyelitis virus can also have a wide host range in nature? My own answer to this question is no. The amount of virus used in the reported tests was so small and the degree of so-called neutralization, therefore, as a rule so slight and so unlike the extensive neutralization produced by the majority of adult human sera, that the results on the animal sera cannot be regarded as specific or indicative of previous infection with poliomyelitis virus. In my own studies with the Lansing virus (in association with Dr. I. Young) it was found that the children on Okinawa developed antibodies for this virus at a very early age, but when eight goats, six horses and nine chickens from the same region were tested against varying amounts of virus, all yielded results which were regarded as negative by comparison with those obtained with the children's sera. Furthermore, Hammon and his associates<sup>51</sup> reported that chickens fed or inoculated with poliomyelitis strains of recent human origin neither excreted virus in the feces nor developed neutralizing antibodies. Also Pearson and his associates<sup>52</sup> have recently reported negative results in their search for virus in the tissues or feces of a large variety of animals present in the environment of human cases of poliomyelitis.

The so-called poliomyelitis-like viruses recovered from rodents, or with the aid of rodents,<sup>53</sup> have added their share of confusion. From a study of all the available data, it is my own considered opinion that the viruses known as MM, FA, GDVII, and related strains are spontaneous encephalomyelitis viruses of rodents, and are no more poliomyelitis-like or related to the poliomyelitis viruses than are the St. Louis, Japanese B, equine and a host of other encephalomyelitis-producing viruses.

The only other creatures from which poliomyelitis virus has been recovered unequivocally in nature, are the nonbiting flies collected in both rural and urban areas during epidemics.<sup>13, 54</sup> The demonstration that flies in an epidemic area can contaminate food with enough virus to transmit the infection to chimpanzees that eat it,<sup>55</sup> has given the nonbiting flies added epidemiologic significance. The recent work of Melnick and Penner<sup>56</sup> strongly suggesting that the flies may not be mere passive carriers but that virus of recent human origin may actually multiply in them and be excreted for three weeks or longer, needs confirmation and extension because of the important bearing it may have on the dissemination of the virus in nature. It may be added here that tests by Hammon,<sup>51</sup> Paul,<sup>54</sup> Francis<sup>52</sup> and their associates on thousands of mosquitoes caught during epidemics of poliomyelitis have all yielded negative results.

Among students of the epidemiology of poliomyelitis there are now three main views on the mode of spread of the disease, all regarding the human being as the primary reservoir of the virus. These views or hypotheses,

for the sake of emphasis, may be called the respiratory, the alimentary, and the alimentary plus the nonbiting flies. The "respiratory" hypothesis postulates that transmission occurs when the virus is breathed out or otherwise expelled from the nose or mouth of one person and is then breathed in by another. The "respiratory" hypothesis is based chiefly on: (1) the demonstrated presence of virus in the pharynx; (2) the conviction, gained from tracing contacts of patients, that the infectious period in poliomyelitis is very short<sup>8, 57</sup> corresponding more to the limited time the virus is present in the throat than to the longer time it is excreted in the stools; and (3) the so-called radial spread of the disease.<sup>57</sup> According to the "alimentary" hypothesis the virus is transmitted by being put into the mouth as by contaminated fingers or food. The "alimentary" hypothesis is based on the following considerations: (1) the stools are the richest potential source of the virus and other infectious agents in excreta are known to be transmitted in a great variety of ways both direct and indirect; (2) the possibility of infection by the oral route has now been established beyond doubt in experiments on animals<sup>13, 31, 33</sup>; (3) studies on other infectious agents have shown that the "nasal" rather than the "pharyngeal" carriers are the "dangerous" carriers,<sup>25</sup> and in the case of poliomyelitis there is no evidence that virus is ordinarily present in the nose<sup>16, 17</sup>; (4) while the virus is present in the pharynx there is no evidence that *under ordinary conditions* it is expelled from the mouth in droplets which could be breathed in by someone else<sup>16, 17</sup>; (5) when virus is breathed in by experimental animals, there is invariably involvement of the olfactory pathway,<sup>58</sup> which is not the case in human beings; (6) "healthy" carriers far outnumber the sick individuals, and the infective period of poliomyelitis cannot definitely be defined as short by tracing contact only to individuals who are sick and therefore largely out of circulation a few days after onset; (7) the phenomenon of radial spread of a human disease can only suggest that the primary reservoir of the infectious agent is in man, and does not indicate one way or another the way it is transmitted.

Neither the "respiratory" nor the "alimentary" hypothesis attempts to account for the fact that 90 per cent or more of the cases and most of the epidemics occur during the late summer and autumn, except for the assumption that hot weather makes the individual more prone to have the paralytic form of the disease. Against this view is the fact that most of the high incidence peaks are in September rather than during the hotter summer months, that when epidemics start late they frequently continue on into October and November, that small epidemics can occur in cold weather, and that the hottest climates have the smallest number of cases with the paralytic form of the disease. The "alimentary plus nonbiting flies" hypothesis regards the predominance of the disease during the late summer and early autumn as being due to greater dissemination of the virus by flies contaminated with infected human excrement. According to this view small



outbreaks can occur in the absence of flies and epidemics can continue at least for a time after the advent of cold weather has caused the flies to disappear, because of the large number of human carriers that are established by the initial widespread dissemination of the virus. The fact that the great improvements in the standards of living and community sanitation during the last half century have instead of lowering the incidence of poliomyelitis tended rather to raise it, and the fact that in the parts of the world where sanitation is of the lowest order and flies in greatest abundance poliomyelitis is a notoriously rare disease, have been brought forward as objections to both "alimentary" hypotheses. Actually, however, there is evidence that in densely populated countries with primitive sanitation poliomyelitis infection is more widespread than elsewhere, although paralytic poliomyelitis which is relatively uncommon among the natives, appears with great frequency among the foreigners in their midst who come from the more hygienic countries,<sup>50</sup> although it is possible that hygiene may have nothing to do with it.

From the point of view of public health practice, it is of considerable importance which of these views is closest to the truth. For according to the "respiratory" hypothesis, you can get the infection without touching anything or anybody or swallowing anything, and the epidemiologic prototype for poliomyelitis is measles and diphtheria. On the other hand, according to the "alimentary" hypothesis you *cannot* get the infection without touching somebody or something contaminated with virus and transferring it with the fingers to the mouth or swallowing food which has been contaminated in any of a great variety of ways. According to the "alimentary plus nonbiting flies" hypothesis intimate person to person contact by itself does not explain the late summer-autumn predominance of the disease, and stresses as an added factor the potential increase in virus dissemination by the nonbiting flies. In both "alimentary" hypotheses the epidemiologic prototype is bacillary dysentery with its inapparent infections, multiple immunologic types, and multiple modes of spread.

I have tried to present to you the available data as critically, and yet as dispassionately, as possible. Nevertheless, I recognize the possibility that I may have overstressed some and understressed others, and that in my limited vision I may have overlooked the truly crucial problems in the natural history of poliomyelitis.

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# ANDROGEN THERAPY \*

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## INTRODUCTION

MANY substances with androgenic properties have been isolated from the testes, adrenals, blood, and urine, but the most potent androgenic material isolated so far is testosterone. This substance was isolated from the testis by Laqueur and his colleagues in 1935<sup>1</sup> and was synthesized in the same year by Ruzicka<sup>2</sup> and Butenandt.<sup>3</sup> Various observations suggest that it is more potent when administered in the form of an ester than when given in the free form. In clinical medicine it is usually administered in the form of the propionate.

Although other androgens have been isolated and prepared synthetically, they are rarely used in clinical medicine and a discussion of androgen therapy is, therefore, concerned primarily with the effects of testosterone.

There is still some debate as to what the male sex hormone actually is, although many observers have considered it to be testosterone in active chemical combination. The functions of other androgens in the body have not been clearly determined, although they may play some rôle in metabolism. For example, the adrenal cortex produces various androgenic materials but we do not know just what their functions in the body are, and in particular whether or not they are normally concerned with the development and maintenance of secondary sex characteristics. Tumors of the adrenal cortex sometimes develop which produce a great excess of androgen, especially dehydroisoandrosterone. In young boys these tumors cause precocious puberty and in sexually mature women cause masculinization, characterized by amenorrhea, atrophy of the breasts, enlargement of the clitoris, hirsutism, lowering of the pitch of the voice, and acne.

Some of the androgenic material isolated from urine comes from the adrenal cortex and the adrenal cortex continues to produce androgenic material after castration.<sup>4</sup> However, the adrenal cortex seems to be unable to substitute for the testis after castration and does not prevent the development of all the signs and symptoms of eunuchism.

## FUNCTIONS OF ANDROGENS

Androgens and estrogens should be looked upon not merely as materials which stimulate sex function, but as general metabolic stimulants which influence the function of all tissues in the body. This point of view can readily

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be appreciated by a consideration of the functions of the sex hormones. The male sex hormone is responsible for the development of the secondary sex characteristics of the male, which include <sup>5</sup>:

1. Growth of the external genitalia.
2. Growth and function of the prostate gland.
3. Increase in the size and firmness of the muscles.
4. Masculine distribution of hair.
5. Lowering of the pitch of the voice.
6. Normal configuration of the skeleton.
7. Normal emotional reactions.

Its influence on the development of the musculature and the skeleton, and on the emotional status of the individual is evidence of its general metabolic effect. During normal puberty the musculature of the male increases in size and firmness. The same changes are observed when puberty is induced with chorionic gonadotropin or testosterone. The quality of the musculature of the male depends on various factors, which include heredity, nutrition, and hormones. An adequate quantity of male sex hormone is essential for the skeleton to attain normal proportions. If it is absent during puberty, the trunk becomes short in proportion to the extremities, the shoulders narrow, and the hips broad. Because of the influence of the male sex hormone on calcium metabolism, its administration has been suggested to promote healing of bone in older men with fractures. The male sex hormone also promotes retention of nitrogen in the body and influences the metabolism of various electrolytes, including sodium and chloride. When administered in large quantities it will cause pitting edema of dependent portions of the body. A very common effect of its administration is the production of acne. It exercises a profound influence on the emotional reactions of men.

Sexually immature men usually have a sense of inferiority and go to great lengths to cover up their physical defect. They also may suffer from depression and have suicidal ideas. When the male sex hormone is suddenly withdrawn from a normal man by castration, similar emotional disturbances may result, as well as atrophy of the genitalia, loss of hair from various parts of the body, decrease in muscle strength, weakness, lack of ability to concentrate and hot flashes.

#### TYPES OF HYPOGONADISM

In order to carry out androgen therapy intelligently, it is necessary to have a clear understanding of the various types of hypogonadism. The testis has two functioning parts, namely, the seminiferous tubules which produce spermatozoa, and the interstitial cells of Leydig, which produce male sex hormone.<sup>6,7</sup> The functions of these two portions of the testis are interrelated and normal spermatogenesis appears to be in part dependent upon normal production of male sex hormone. However, these functions may

vary independently and the testis may show atrophy of the seminiferous tubules without much impairment of function of the interstitial cells.

It has been suggested by some observers, including Törnblom<sup>8</sup> and McCullagh,<sup>9</sup> that the testis produces a second hormone which is estrogenic in nature and is elaborated by the seminiferous tubules.

There is a close relation between the anterior lobe of the pituitary and the testis. The anterior lobe of the pituitary produces a follicle-stimulating hormone which influences the function of the seminiferous tubules and a luteinizing hormone which stimulates the interstitial cells to produce male sex hormone. Hypogonadism may therefore be either primary or secondary, the primary type being caused by some defect in the testis itself, and the secondary type being the result of some defect in the stimulating mechanism in the pituitary. These two types of hypogonadism, on theoretical grounds, may be further subdivided as follows:

#### PRIMARY TYPE

1. Hypofunction of the seminiferous tubules without impairment of the interstitial cells.

2. Hypofunction of the interstitial cells without impairment of the function of the seminiferous tubules.

3. Hypofunction of both portions of the testis.

#### SECONDARY TYPE

1. Deficient production of follicle-stimulating hormone, affecting primarily the seminiferous tubules.

2. Defective production of luteinizing hormone, affecting primarily the interstitial cells.

3. Defective production of both follicle-stimulating and luteinizing hormones, affecting the function of both portions of the testis.

Theoretically, all of these types of hypogonadism may be present, but in most instances when there is a deficient function of one portion of the testis, there is some evidence of a deficient function of the other. It is not uncommon to observe atrophy of the seminiferous tubules and azoospermia in men whose testes produce enough male sex hormone to maintain secondary sex characteristics. The opposite of this condition, namely, normal function of the seminiferous tubules with deficient function of the interstitial cells is theoretically possible, but has rarely been observed.

#### STIMULATION AND SUBSTITUTION THERAPY

Androgen therapy is substitution therapy whereas gonadotropic therapy is stimulation therapy.<sup>5</sup> Androgens should be employed when it is impossible to stimulate the testis adequately with gonadotropins. Chorionic gonadotropin is a very effective material for stimulation of the interstitial cells of the testis, but does not have much influence on the function of the seminiferous tubules. Pituitary and equine gonadotropins theoretically

stimulate the functions of both portions of the testis, but primarily the function of the seminiferous tubules, because they contain an excess of follicle-stimulating hormone. In actual practice they are not very effective, and we therefore do not have any satisfactory method of stimulating spermatogenesis when it is deficient.

### USES OF ANDROGENS

Androgen therapy appears to be of value in the following conditions<sup>6</sup>:

1. Eunuchism.
2. Primary eunuchoidism.
3. Bilateral intra-abdominal cryptorchism.
4. The Fröhlich syndrome associated with intra-abdominal cryptorchism.
5. Pituitary dwarfism.
6. Carcinoma of the breast.
7. Functional uterine bleeding.
8. Suppression of lactation.
9. Impotence from glandular causes.
10. The male climacteric.
11. Fractures in old men.
12. Cushing's syndrome.
13. Addison's disease.
14. Hypopituitarism with secondary hypogonadism in old men.

### EUNUCHISM

In eunuchism there is complete loss of all functions of the testis as a result of removal, injury, or atrophy. The intramuscular administration of testosterone propionate in oil usually substitutes completely for the male sex hormone. The effects of its administration depend somewhat upon the age at which treatment is carried out. If an individual is castrated during childhood, the administration of testosterone propionate during the age of puberty will cause normal development of the secondary sex characteristics, including growth of the genitalia, development of the musculature, normal configuration of the skeleton, lowering of the pitch of the voice and growth of hair on the body.

If an individual is castrated during childhood and treatment is delayed until after the age of puberty, some skeletal disproportion persists and the genitalia, musculature, and hair cannot be made to develop as much as if the stimulus is applied during the age of puberty. Testosterone propionate is effective throughout life, and even if treatment is delayed until the age of 60 years, a considerable amount of development of secondary sex characteristics can be induced. The ideal age to begin treatment in eunuchs is 11 or 12 years. The defect is a permanent one and such individuals require treatment throughout life. The amount of material required to produce maximum



development varies in different patients but in many, maximum development can be induced with 25.0 mg. given intramuscularly three times a week. In some instances as much as 50.0 mg. a day may be necessary.

When men are castrated after the age of puberty, the administration of testosterone propionate will restore the secondary sex characteristics to normal.

### PRIMARY EUNUCHOIDISM

In eunuchoidism there is only partial loss of testicular function. There is always a deficient production of male sex hormone, and almost always a deficient function of the seminiferous tubules. It may be associated with bilateral cryptorchism or atrophic testes may be present in the scrotum. Whether it is primary or secondary in nature can be determined by an assay of the follicle-stimulating hormone in the urine. If this is present in normal or increased quantities, it may be assumed that the primary defect is in the testis and that the function of the pituitary is normal. If it is present in deficient amounts, it may be assumed that the primary defect is in the pituitary and that the testis is not properly stimulated.

If facilities for hormone assays are not available, the type of eunuchoidism may be determined by the administration of chorionic gonadotropin. If the testis responds to stimulation therapy it may be assumed that the eunuchoidism is of the secondary type; and, if it does not respond, that it is of the primary type. It is a good general rule to observe the effect of stimulation therapy before resorting to substitution therapy with androgens. In many patients with eunuchoidism, after the age of puberty, the testis may show a definite response to stimulation therapy with chorionic gonadotropin, but may not produce enough male sex hormone to cause adequate development of the secondary sex characteristics. Under these circumstances treatment with testosterone propionate may be desirable even though the eunuchoidism is of the secondary type. It is possible that in these patients irreparable damage to the testes occurs as a result of the long period of absence of adequate stimulation.

The treatment of the eunuchoid state should be started at the age at which puberty normally begins, namely, 11 or 12 years. If the testes are in the scrotum it is not always easy to be certain at this early age that the function is deficient, and for this reason treatment is often delayed until irreparable changes in the skeleton and musculature occur. In eunuchoid individuals the testes are usually abnormally small even before puberty. When the testes are in the abdominal cavity, an effort should be made to bring them into the scrotum by treatment with chorionic gonadotropin or testosterone propionate. The actual type of treatment used depends upon whether or not the testes can respond to stimulation therapy. After the testes have been brought into the scrotum, further treatment may be delayed until the age of puberty.

It is recommended that the testes be brought into the scrotum as early as possible because they cannot function normally in the abdominal cavity and after they have been brought into the scrotum they may be able to respond more readily to stimulation therapy. The risk of permanent damage to the testes appears to be greater the longer they remain in the abnormal environment of the abdomen.<sup>10</sup>

### BILATERAL INTRA-ABDOMINAL UNDESCENDED TESTES

In most patients with undescended testes, chorionic gonadotropin is the best therapeutic agent. It may produce definite stimulation of genital growth even when both testes are in the abdominal cavity. This material should, therefore, be used first and the administration of testosterone propionate resorted to only if chorionic gonadotropin is ineffective. In some instances intra-abdominal testes will descend into the scrotum with glandular therapy, but very often surgical measures are necessary after some stimulation of genital growth has been produced with chorionic gonadotropin or testosterone propionate.

### THE FRÖHLICH SYNDROME AND UNDESCENDED TESTES

In most patients with the Fröhlich syndrome the testes are in the scrotum, but they are undescended in patients with this disorder more commonly than in normal individuals. In patients with the Fröhlich syndrome in whom both testes are in the abdominal cavity, treatment with chorionic gonadotropin should be tried first and testosterone propionate used if it is ineffective.

Patients with bilateral intra-abdominal cryptorchism may have hypogonadism of the primary or secondary type and the cryptorchism may be caused by mechanical or glandular factors. If the testes fail to function properly when they are brought into the scrotum, glandular therapy of the stimulation or substitution type must be continued indefinitely, the form of therapy depending upon the type of hypogonadism which is present. The dose of chorionic gonadotropin required varies from patient to patient, but in most instances the intramuscular administration of 500 I. U. of this material three times a week is adequate. The dose of testosterone propionate that is required also varies from patient to patient, but in most instances 25.0 mg. administered intramuscularly three times a week will cause complete development of secondary sex characteristics.

### PITUITARY DWARFISM

Testosterone propionate is a very potent stimulator of genital growth. When androgens are present in large quantities in young boys, either as the result of tumors of the adrenal or testis, or as the result of therapeutic administration, they cause rapid growth of the skeleton in length and affect the skeletal proportions. Young boys with tumors of the adrenal cortex, which

produce an excess of androgens, grow rapidly in height and for a few years are taller than most boys of their age. Eventually they become somewhat short in stature because of the premature closure of their epiphyses. The administration of chorionic gonadotropin, which stimulates the testes to produce androgenic material, also causes rapid growth in height in young boys.

Because of its growth promoting properties, testosterone propionate is of definite value in the treatment of pituitary dwarfism. It stimulates that component of growth associated with puberty, but is not a substitute for the growth hormone of the pituitary or for the thyroid hormone, without which the skeleton cannot become normal in length. In other words, the pituitary dwarf who is treated with testosterone propionate at the proper age, grows taller and develops proper proportions between various parts of his skeleton. The maximum amount of growth in height which we have observed during the administration of this material to a pituitary dwarf is ten inches. The individual remains a dwarf, but does derive the benefit of the growth that is associated with the onset of sexual maturity. The growth promoting properties of testosterone propionate are of great practical importance because of the fact that there is no effective preparation of the growth hormone of the pituitary available at the present time. The stimulation of genital growth in pituitary dwarfs is necessary only when there is deficient production of pituitary gonadotropins, as well as of pituitary growth factor, and the treatment should be started at the age at which puberty usually gets under way, namely, at the age of about 12 years.

The hypogonadism associated with hypopituitarism is of the secondary type and the administration of chorionic gonadotropin is, therefore, usually effective in stimulating skeletal growth in pituitary dwarfs. Testosterone propionate needs to be used only when a maximum effect cannot be produced with chorionic gonadotropin.

#### CARCINOMA OF THE BREAST

There have been two very interesting developments in the relation of hormones to cancer. These developments concern carcinoma of the prostate and carcinoma of the breast. A few years ago Huggins<sup>4,11</sup> reported that surgical castration and functional castration with stilbestrol produced a very striking improvement in patients with carcinoma of the prostate. The lesion in the prostate diminished in size, the metastases in bone became calcified, and, in some instances, the roentgen-ray evidence of metastases disappeared. There was an associated disappearance of pain and great improvement in the general nutritional state of the individual. Of the original 20 patients reported by Huggins, four were alive six years after surgical castration and showed no evidence of metastases.

In many patients, following initial improvement, relapse was noted and they proceeded to die of cancer of the prostate. To explain this phenomenon, Huggins<sup>4</sup> has suggested that the cancer cells, in many in-

stances, take on androgen independence and that, while androgenic material may be necessary initially for the growth of the cancer cells, they eventually become independent of this stimulation. These observations are of great interest, but it is obvious that androgen stimulation alone will not result in the development of cancer of the prostate. Some factor must be present in the cells themselves, which makes them undergo malignant degeneration under the influence of this stimulus.

The hormonal status in cancer of the breast is similar to that in cancer of the prostate.<sup>12, 13, 14, 15, 16</sup> Many years ago it was noted that women with cancer of the breast often showed some improvement following removal of the ovaries. Recently it has been observed that the administration of testosterone propionate in large doses causes definite amelioration of symptoms in patients with this disorder. It does not have much effect on the lesion in the breast, but seems to be effective in bone metastases, regardless of the age of the patient. It causes some calcification of the metastases, causes the pain to disappear, and improves the nutritional status of the patient. The mechanism of this action in older people is not easy to understand. In women before the age of the menopause, it could be considered the result of suppression of ovarian function. For some reason which is not clear at the present time, estrogenic therapy causes a diminution in the local lesion in the breast and in soft tissue metastases in women after the age of the menopause. This effect is not easy to understand if the development of carcinoma of the breast is the result of estrogenic stimulation, but there does not appear to be much doubt about the fact that improvement occurs with this type of treatment in older women. On the other hand, estrogenic therapy is said to be contraindicated in women with carcinoma of the breast before the age of the menopause. The improvement which follows glandular therapy in women with carcinoma of the breast is less striking than the improvement which follows glandular therapy in men with cancer of the prostate and most patients, after initial improvement, die of carcinoma of the breast. The dose of testosterone propionate required to produce improvement is approximately 100 mg. three times a week. This amount of material is given over a period of eight to ten weeks, following which smaller amounts of material may be used. Androgenic therapy in these doses produces some masculinization, but masculinization can be tolerated provided the symptoms of cancer are ameliorated and life expectancy increased. It should be emphasized that glandular therapy is indicated only in the treatment of inoperable cancer of the breast. The treatment of choice in all patients with operable carcinoma is radical mastectomy.

#### FUNCTIONAL UTERINE BLEEDING

It is generally agreed that the administration of testosterone propionate is of definite value in controlling functional uterine bleeding. Before resorting to such treatment the patient must be carefully examined in order to make

sure that the bleeding is functional in origin. Tumors and other anatomic abnormalities in the uterus and blood dyscrasias must be excluded. It is very desirable to use the smallest amount of material that will control the bleeding, in order not to cause masculinization. Methyltestosterone may be given by mouth. The effective dose varies from patient to patient. It is claimed that women will tolerate as much as 300 mg. of methyltestosterone per month without undergoing masculinization.

### SUPPRESSION OF LACTATION

It has been reported that androgenic therapy is of value in suppressing lactation following childbirth. Similar improvement has also been claimed as a result of the administration of various estrogens. It is thought that both androgenic and estrogenic material influence lactation by suppressing pituitary function. As in the case of functional uterine bleeding, it is very important to use small amounts of testosterone so that masculinization will be avoided.

### IMPOTENCE FROM GLANDULAR CAUSES

Impotence associated with definite hypogonadism is promptly relieved by the administration of testosterone propionate or chorionic gonadotropin, the form of treatment depending upon whether the hypogonadism is primary or secondary in type. In many patients impotence is neurogenic or psychogenic in origin and is not corrected by glandular therapy. If adequate laboratory facilities are available for hormone assays, it is possible to determine whether hypogonadism is present or not. If such facilities are not available, stimulation or substitution therapy may be tried, according to the type of hypogonadism which appears to be present. If improvement occurs it usually means that the impotence is associated with a glandular deficiency. Occasionally patients in whom there is an important neurogenic or psychogenic factor will show some improvement with glandular therapy.

### THE MALE CLIMACTERIC

There is a great deal of debate as to whether or not there is such a disorder as the male climacteric. There is no definite epoch in the male like the menopause in the female, and climacteric changes are certainly much less common in the male than in the female. However, there appears to be little doubt that in some men a definite decrease in the production of androgenic material occurs as they grow older and that this decrease is sufficient to produce symptoms which are similar to those observed in the menopause of the female and include hot flashes, ease of fatigue, irritability, palpitation and depression. These changes are often associated with an increase in the secretion of follicle-stimulating hormone in the urine, although the laboratory evidence for the diagnosis of the male climacteric is not very clear cut.

Great caution should be exercised in making the diagnosis and it should be arrived at only after the most careful examination of the patient and after every other possible cause for the symptoms has been excluded. When the condition definitely exists the administration of testosterone propionate in a dose of 25.0 mg. intramuscularly three times a week causes amelioration of the symptoms.

### FRACTURES IN OLD MEN

Because of the influence of testosterone propionate on the growth of bone and on the deposition of calcium in bone, the administration of this material may be of value in old men with fractures. A sufficient number of observations have not been made to prove the efficacy of this form of treatment beyond doubt, but a few observations have been made by reliable investigators. Similar improvement has been reported in older women with fractures as a result of the administration of estrogenic material, which also influences the growth of bone.

### CUSHING'S SYNDROME

In some patients with Cushing's syndrome there is an excessive loss of nitrogen in the urine and under these circumstances the administration of testosterone propionate may be of value because it promotes retention of nitrogen. It does not cure the disease, but in some instances may produce a great deal of improvement temporarily.

### ADDISON'S DISEASE

The administration of androgenic material has been recommended in the treatment of Addison's disease in both the male and female. In Addison's disease the adrenal cortex is usually completely destroyed and this source of androgenic material in the body is therefore lost. We have not observed its effect in the female but, in our experience, in the male the administration of testosterone propionate, in addition to specific therapy, often produces more improvement than specific therapy alone.

### HYPOPITUITARISM WITH SECONDARY HYPOGONADISM IN OLD MEN

In most patients with hypogonadism secondary to hypopituitarism, chorionic gonadotropin is the material of choice for the correction of the hypogonadism. In older men the testis does not respond as well to stimulation therapy and the administration of testosterone propionate is indicated.

### MISUSES OF ANDROGENIC THERAPY

The administration of testosterone propionate is either contraindicated or of no value in the following conditions:

1. Sterility.
2. Benign prostatic hypertrophy.

3. Carcinoma of the prostate.
4. The Fröhlich syndrome with one or both testes in the scrotum.
5. Undescended testes, unless there is no response to stimulation therapy with chorionic gonadotropin.
6. Impotence, if not glandular in origin.
7. Arteriosclerotic or hypertensive heart disease in old men.

In large doses testosterone propionate may depress testicular function and cause an actual azoospermia. In moderate doses it does not appear to have this effect and may have a beneficial effect on spermatogenesis. In most instances it is of little value in stimulating spermatogenesis in sterile men.

Testosterone propionate has been reported to produce some improvement in men with benign prostatic hypertrophy, but careful search for objective signs of improvement by several investigators has resulted in the conclusion that it is of little or no value. The male sex hormone is responsible for the development of the prostate and it is difficult to see how the administration of this material would reduce its size. It may possibly in some instances produce a little improvement by increasing the tone of the muscle of the bladder.

In view of the possible rôle which androgens may play in the development of carcinoma of the prostate, it is unwise to administer androgens to any man who is suspected of having this disorder.

The status of glandular therapy in the Fröhlich syndrome, undescended testes, and impotence has already been discussed.

In old men with arteriosclerotic and hypertensive heart disease, androgen therapy may increase the risk of a vascular accident by increasing muscle activity. The danger is not very great, but should always be borne in mind.

#### CONDITIONS IN WHICH ANDROGENIC THERAPY IS OF DOUBTFUL VALUE

1. Angina pectoris.
2. Homosexuality.
3. Dysmenorrhea.
4. Carcinoma of the ovaries.

Lesser<sup>17</sup> reported definite improvement in about 50 per cent of the patients with angina pectoris following the administration of testosterone propionate. The improvement appeared about six to eight weeks after the administration of the material was started. Other reports have appeared concerning the use of this material in angina pectoris, but the evidence of improvement is not convincing.

Glandular therapy has not proved very effective in the treatment of homosexuality. Testosterone has been administered intramuscularly in large doses to homosexual men without improvement in most instances. Occasionally slight improvement occurs, but the results on the whole are dis-

appointing. Negative results have also been obtained with the use of estrogenic therapy in homosexual females. Sometimes the administration of stilbestrol to homosexual males will reduce their interest in members of the same sex, by suppression of testicular function. Estrogenic therapy must be administered cautiously to males because of its feminizing effects, including enlargement of the breasts.

The administration of testosterone propionate has been reported to be beneficial in some women with dysmenorrhea. The data are not extensive enough to warrant definite conclusions. Estrogenic material has also been reported to produce improvement and would certainly be the material of choice because of the risk of inducing masculinization with androgenic therapy. Dysmenorrhea is a complicated disturbance and involves neurogenic and psychogenic factors, as well as glandular factors.

Androgenic therapy has also been recommended in the treatment of after-pains and engorgement of the breasts. It may be of some value in reducing engorgement of the breasts following childbirth, but it has not been tried on a sufficiently large scale in these two conditions to justify any conclusions concerning its value.

#### HARMFUL EFFECTS OF ANDROGEN THERAPY

1. Injury to the normal testis, with production of azoospermia.
2. Acne vulgaris.
3. Masculinization in women.
4. Pitting edema of the lower legs.
5. Hypermetabolism.

*Injury to the Normal Testis.* The administration of large doses of testosterone propionate, such as 50.0 mg. per day, may produce an azoospermia in a man with a normal spermatozoa count. Histologically, there is a striking effect on the seminiferous tubules. Following the omission of treatment the seminiferous tubules recover and the spermatozoa count returns to normal. It has not been demonstrated whether or not permanent damage can be produced by the prolonged administration of large doses. In moderate doses, such as 25.0 mg. three times a week given intramuscularly, testosterone propionate does not appear to reduce the spermatozoa count, and in small doses may actually have a beneficial influence on spermatogenesis because of the close relationship that exists between the functions of the two portions of the testis.

*Acne Vulgaris.* The administration of testosterone propionate to men or boys commonly causes acne, the extent of which depends upon the size of the dose and some individual susceptibility of the skin of the patient. Acne can also be produced in young boys by the administration of chorionic gonadotropin, which stimulates the production of male sex hormone. Acne appears without treatment at puberty when the production of androgenic material increases. There seems to be little doubt that there is a close cor-



relation between the concentration of androgenic material in the body and the development of acne vulgaris.

*Masculinization in Women.* As already pointed out, the administration of testosterone propionate in fairly large doses produces masculinizing effects in women, which include lowering of the pitch of the voice, development of hair in masculine areas, atrophy of the breasts, amenorrhea, decrease in vaginal secretion, and enlargement of the clitoris. These effects are undesirable and whenever androgenic therapy is indicated in the female, every effort should be made to employ a dose which does not produce them. Masculinizing effects cannot be avoided in the treatment of women with inoperable carcinoma of the breast.

*Pitting Edema of the Lower Legs.* Testosterone propionate promotes retention of nitrogen, sodium, and chloride, and when given in large doses often causes pitting edema in the lower legs. In moderate doses, which are adequate to induce sexual maturity in immature men, namely, 25.0 mg. three times a week, it usually does not produce this effect.

*Hypermetabolism.* During the administration of 50.0 mg. of testosterone propionate daily by intramuscular injection, the basal metabolism may rise as much as 35 to 40 per cent above normal. The administration of methyltestosterone by mouth in large doses will also cause a striking rise in basal metabolism. The mechanism of this action is not known, and in particular, it is not known whether it is the result of a direct effect on the metabolism of tissues or whether it is the result of some action on the pituitary or thyroid. Individuals who show an increase in metabolism during androgenic therapy do not present symptoms suggestive of hyperthyroidism. In doses of 25.0 mg. three times a week the basal metabolism is usually not affected.

#### METHODS OF ADMINISTRATION

Testosterone may be administered in the following ways:

1. Intramuscularly in the form of testosterone propionate.
2. Subcutaneously in the form of pellets.
3. Intramuscularly as a suspension of free testosterone in water.
4. By mouth in the form of methyltestosterone.

For the production of maximum changes the intramuscular administration of testosterone propionate appears to be most effective. Pellets have not been used very extensively and further work should be done in order to determine whether or not they will produce maximum masculinizing effects. They may be of value for maintenance therapy after maximum changes have been induced by the intramuscular administration of testosterone propionate. Free testosterone suspended in water is of value when administered intramuscularly, but there are not enough data to state the relative effectiveness of this method of treatment, as compared with the intramuscular administration of testosterone propionate. Methyltestos-

terone produces a definite effect when administered by mouth, but is not as effective as testosterone propionate given intramuscularly. Like pellets, it may be of value for maintenance therapy.

### SUMMARY

This article presents a resumé of the uses, misuses, and harmful effects of androgenic therapy, and a discussion of the conditions in which androgen therapy is of doubtful value.

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# THE PHYSIOLOGIC EFFECTS OF PHYSICAL THERAPY \*

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DURING the past 10 years interest in physical medicine has increased markedly. In spite of this physicians continue to show considerable scepticism as to the advantages of this form of therapy. This attitude is due in no small measure to the belief that physical medicine does not rest upon a sound physiological basis. The purpose of the following remarks is to point out that the most useful and commonly employed procedures in physical medicine, i.e. the use of various forms of heat and cold, massage, and therapeutic exercise, depend for their effectiveness upon well established physiological reactions. A thorough understanding of these reactions is as essential to the successful use of physical therapy as is correct diagnosis, accurate anatomic knowledge of the involved part, and familiarity with various technics.

## HEAT

Heat, in some form, applied generally or locally, represents the therapeutic measure most frequently used in any department of physical medicine. A summary of one year's experience in a general hospital showed that of 23,345 treatments given in the department of physical medicine heat was a feature in 44.3 per cent of cases. Next to heat came massage, 34 per cent, and then therapeutic exercise, 15.4 per cent. The value of heat in the management of many conditions, based upon clinical observation, appears to be well established. In spite of the widespread employment of heat as a therapeutic agent and extensive physiological studies on the effects of heating, the complex changes that are induced when human beings are subjected to heat are still imperfectly understood. Their solution awaits further investigation.

Briefly it may be stated that the most important effect of the systemic application of external heat is to increase body temperature. Regardless of the method employed the fever thus produced is the result of creating a disproportion between heat production and heat dissipation. The degree to which temperatures may thus be elevated depends upon the duration and amount of heat energy input and the efficiency with which output is controlled. Phenomena which accompany the induction of fever consist of an increase in pulse and circulatory rates. According to Krusen and Elkins,<sup>1</sup> both the volume output of the heart and the velocity of the blood may be increased up to 400 per cent. Marked peripheral vasodilatation occurs. The

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respiration is accelerated. The rise in temperature is usually associated with sweating. When this is profuse and not offset by adequate fluid administration, reduction in blood volume occurs which may be sufficient to bring about peripheral vascular failure. Dehydration and hyperventilation induce alkalosis which at times reaches a critical level. There are no significant changes in either the nitrogenous or non-nitrogenous constituents of the blood, except that with profuse sweating the blood chlorides are decreased. The red cell count is altered but little. After the febrile reaction is established the leukocyte count rises and there is a relative increase in neutrophils and decrease in lymphocytes.<sup>2</sup> Hartman<sup>3</sup> has pointed out that a serious effect of induced fever may be anoxemia. The value of prolonged hyperthermia in combating certain infections (notably luetic and gonococcal) depends upon the bactericidal effect of the fever as well as the stimulation of the defense mechanisms of the body against disease.

Observations recently carried out by Horvath and Botelho at the University of Pennsylvania furnish data on some physiological reactions that are brought about when individuals are placed under the abnormal stress of heat, regardless of whether it is used in its positive aspect, as a hot bath, or in its negative aspect, as a cold bath.

They employed 19 subjects, seven males and 12 females. Their average age was 28 years and all of them were in excellent physical condition. After a control period of rest during which repeated observations were made on heart rate, blood pressure and cardiac output, the subject was immersed to the neck for 20 minutes in a tank of water maintained at a temperature of either 18° C. or 40° C. Heart rates were obtained every minute, blood pressure every two minutes during the immersion. After removal from the bath the subject was observed for at least 20 minutes and in some instances for one hour. Cardiac output, heart rate and blood pressure were again repeatedly recorded. Oral and rectal temperatures were taken immediately and 30 minutes after the bath.

Twenty-two experiments were conducted on 17 subjects with hot baths. The observers found that the body temperature rises appreciably following immersion in a bath of 40° C., namely 37.6° to 38.4° or a mean increase of 0.8° C. This is a rate increase of 2.4° C. per hour. Oral temperatures in general showed a similar rise. A half hour after removal from the bath the rectal temperatures were still elevated and in a few individuals it had not returned to normal levels for over an hour.

During the bath the heart rate was increased in the first minute after immersion. At the end of 20 minutes it was approximately 50 per cent greater than the control level. As a result of a lower diastolic pressure pulse pressure also increased. Immediately after the hot bath the heart rate began to return to normal, although it required some 20 minutes before control levels were attained. Cardiac output one minute after the bath was found to be increased in all subjects, the average rise being 42 per cent.

Fourteen minutes after the bath cardiac output in eight subjects had returned to normal, but it was still elevated in the remaining subjects as much as 40 per cent. This increased cardiac output was associated with rapid heart rate, in some instances double the control value. It was concluded that the increased cardiac output was primarily due to the higher heart rate, since the average stroke volume did not differ from control values.

Only 11 subjects were available for exposure to baths of  $18^{\circ}\text{C}$ . Shivering occurred in all but one case. The rectal temperature dropped on an average of  $0.1^{\circ}\text{C}$ . during the bath. The shivering, a defense reaction, was doubtless a factor in maintaining the level of heat production. A more significant drop in temperature occurred a half hour after removal from the cold bath. At this time in all subjects it fell at least  $0.2^{\circ}\text{C}$ . below the values obtained immediately after the bath. After the first half hour body temperature began to return to control levels.

The first two minutes after immersion in cold water the systolic pressure rose rapidly, the result of initial vaso-constriction. At this time shortness of breath was also marked. Following these early changes subjects were able to relax and systolic blood pressure returned to approximately control values, although the heart rate continued to rise. During the post-bath observation period there was a slowing of the heart rate. In the first minute after the  $18^{\circ}\text{C}$ . exposure cardiac output was reduced. Fourteen minutes later it was below control values in all subjects, showing an average decrease of 10 per cent.

Since the thermal stimuli used in these experiments were so mild that the organism was able to make and maintain adequate adjustments, Horvath concluded the degree of stress induced could be more completely evaluated if individuals were subjected to an added stress-producing stimulus. Change in posture was, therefore, imposed upon the stimulus of the hot or cold bath. Position was changed alternately from supine to erect passively by means of a tilting ballistocardiograph. In each position heart rate and blood pressure and cardiac output were measured. After these pre-bath observations the subject was immersed to the neck for twenty minutes in a bath with a temperature of either  $18^{\circ}\text{C}$ . or  $40^{\circ}\text{C}$ . Upon completion of the bath the subject was returned to the ballistocardiograph and observed through two supine and two erect periods in the same manner as during the control period.

Approximately one-half of the subjects developed orthostatic hypotension following immersion for 20 minutes in a bath of  $40^{\circ}\text{C}$ . Based upon the post-thermal orthostatic responses they divided their subjects into three groups: (1) the syncopal, (2) the abnormal, and (3) the normal. The syncopal group included four individuals who, when upright, developed typical symptoms and signs of syncope of varying intensity. No evidences of syncope or distress were observed after the hot bath in any individual while kept supine.

Ten subjects were subjected to postural stress after being exposed to the cold bath. The only difference in response observed was that in erect position after the bath the increase in heart rate was only minor compared with that noted from the pre-bath or control tilt.

These observations on the effects of hot baths, especially when they are combined with postural change, furnish an explanation for the not infrequent occurrence of syncope after prolonged hot baths. They further emphasize the importance of a period of rest in the recumbent position following exposure of the body to unaccustomed prolonged heating.

The local application of heat continues to be one of the most readily available procedures in physical therapy. The commonest methods of applying heat are by conduction, when an exchange of molecular energy is brought about by direct contact and by convection, when the source of heat is hot water, hot air, or the infra-red radiant energy derived from lamps or reflectors. All of these forms of heating are relatively inefficient and slow and their penetration slight. The radiant energy produced in the near infra-red range is the most penetrating and produces some rise in temperature of the subcutaneous tissue after prolonged exposure.

An effective procedure which raises the temperature of the deeper tissues is the conversion of alternating electric currents of high frequency into heat. This method of heat production is referred to as short wave diathermy. Either a condensor field or an induction field can be employed in the production of heat by short wave diathermy.

Under ordinary conditions the physiological effects brought about by the local application of heat, regardless of the method employed, consist of increased local circulation characterized by vaso-dilatation, a rise in capillary pressure, acceleration of the transfer of fluid from the blood to the tissues and an increase in local metabolic activity and probably phagocytosis. As a rule, an excessive concentration of heat in the tissues is prevented by increased blood flow which distributes the heat throughout the body. However, recent experimental work on the rate of blood flow in animals treated with short wave diathermy raises some doubt as to whether this mechanism is operative under such conditions.

Mart and Miller <sup>4</sup> measured the rate of blood flow through the coronary vessels before, during and after the application of short wave diathermy over the heart and noted no significant increase in the flow of blood. Kemp, Paul and Hines <sup>5</sup> found that the femoral arterial inflow into the hind leg of dogs was reduced when the limb was treated with diathermy. This reduction was noted whether the limb treated was denervated or not denervated. Heretofore it has been generally stated that diathermy causes an increase of blood flow in the deeper structures. From these observations the thought arises that, since such is apparently not the case, at least in part some of the rise in temperature of the deeper structures that is induced by diathermy is due to a decrease in the flow of blood to the heated tissue.

In the course of a discussion of the physiological effects of heat Horvath<sup>6</sup> states that two factors must always be considered in heat therapy, (1) the amount of heat successfully applied into the tissues, and (2) the extra amount of heat produced in the tissue as a consequence of the oxidation processes that have been accelerated by the heat applied. These factors deserve careful consideration when heat therapy is contemplated.

The realization of the importance of this principle brought about a radical change in attitude towards the use of heat in patients suffering from impaired peripheral circulation. All forms of heat in even moderate degree are dangerous to ischemic limbs. When arterial flow is obstructed, or even diminished, exposure to even mild temperatures of from 80° to 90° F. can cause an increase in metabolism which demands more oxygen than is available when arterial flow is inadequate. Thus a relative ischemia develops which induces increased pain and leads to edema, ulceration and gangrene. When vasodilatation in an extremity is desirable, reflex dilatation of vascular channels may be brought about by heating some other part of the body and thus avoiding disturbance of the metabolism of the affected extremity. This was demonstrated by Landis and Gibbons.<sup>7</sup> Intact sympathetic innervation of the part is essential if this procedure is to be effective.

The same principle applies when obstructive lesions of the venous circulation are present. With the arterial channels open the demand for additional blood created by heating can be met. However, with the venous return flow impaired adequate cooling and heat dissipation are so interfered with that the temperature of the tissue rises to levels which bring about edema and ulceration. It is in these peripheral vascular lesions that cooling and even mild refrigeration, which tend to lessen circulatory demands and diminish metabolic activity, have proved a more effective form of physical therapy than heat.

In certain inflammatory conditions, notably the more acute stages of arthritis or trauma such as sprains and fractures in their early stages when frank or latent edema is present, it is a common clinical observation that the local application of heat, and especially the deep heating induced by diathermy, aggravates the pain and swelling. The explanation is that, if heat locally increases tissue fluid exchange, the already present tissue fluid accumulation is increased to the point where pressure on the venous channels and lymphatics interferes with the return circulation.

Ordinary methods of applying heat therapeutically are slow and ineffective in raising deep tissue temperatures. Short wave diathermy alone is capable of bringing about deep heating with any degree of rapidity. In order to meet the need for some method of causing rapid, deep, localized heating of tissue there has recently been developed a device by which human tissue may be heated by microwave radiation. The instrument generates energy in a continuous wave, air-cooled, magnetron oscillator tube which operates at a frequency of 2400 to 2500 megacycles or at a wave length of

approximately 12 cm., with a maximum power output of 125 watts. It will be recalled that the development of the magnetron oscillator tube made possible radar, which played such an important part during the war. Now its usefulness has been extended to the field of medicine.

At the direction of the Council on Physical Medicine of the American Medical Association the new apparatus has been investigated by Stafford L. Osborne and Jesse N. Fredericks of the Department of Physical Medicine and Physiology of Northwestern University Medical School.<sup>8</sup>

Of the several investigations that are being carried out on the effects of the high frequency current of this magnitude on human beings, those of Horvath, Miller and Hutt of the Department of Physical Medicine, University of Pennsylvania, will be discussed.<sup>9</sup>

These investigators have studied nine subjects, six males and three females, varying in age from the early twenties to the late sixties. In order to measure the deep and superficial tissue temperatures, needle thermocouples were inserted into the thigh. Temperature readings were recorded at the surface, at a depth of 4 to 13 mm. in the subcutaneous tissue, and in muscle at a depth of 30 mm. or over. Control observations were made before the application of the radiation. Thermocouples were then removed from the area to be treated. Immediately after a 15 or 30 minute exposure in the radiation field of a microwave generator with a magnetron tube oscillating at a frequency of 2450 megacycles per second and a wave length of 12.2 cm., thermocouples were replaced and the cooling of tissues was observed for a period varying from 30 to 130 minutes. A power output of 50 watts was used most often because of the frequency with which this dosage has been employed in clinical trials of this mode of therapy.

The application of this form of high frequency, electrical energy caused no discomfort to the patients treated, who reported only a pleasant sense of warmth and were not conscious of the high internal temperatures developed. The lack of subjective discomfort presents a certain element of danger because it leads patients, as well as operators, to believe that only a small amount of heat is being generated and creates the desire to increase the power output which might well bring about serious effects on the deep tissues.

The findings of Horvath and his associates in general correspond to the results that have been obtained by Krusen, Herrick, Leden and Wakim<sup>10</sup> and Osborne and Fredericks.<sup>11</sup> Horvath's summary is as follows: "The employment of high frequency electrical energy in a 12 centimeter band (2450 megacycles per second of the electro-magnetic spectrum) provides a means of selectively heating local masses of tissue. The magnitude and depth of heating may be altered by varying directors and the power output of the generator. Maximal temperatures observed following a 15 minute period of heating, utilizing a power output of 50 watts with a six-inch director, were 36.4° C. at the surface, 44° C. at subcutaneous levels and 40° C. in muscle tissue. In the majority of experiments the temperature gradient from sub-



cutaneous tissue to muscle to surface was not modified greatly as a consequence of this mode of heating. However, in a large number of instances the subcutaneous and muscle gradient was reversed. High internal temperatures were secured with only incidental elevation of surface temperatures. No increase in rectal temperatures was observed."

At the present time Horvath et al. are studying the effects of microwave on blood flow. Krusen and others have reported a definite increase in the circulation of the heated extremity in both experimental and clinical study. Much careful clinical observation must be carried out before the therapeutic value and harmlessness of the microwave on human beings is firmly established.

In recent years no subject in physical medicine has evoked more discussion and controversy than the use of hot packs in the treatment of acute and subacute poliomyelitis. In spite of the extensive use of this now popular procedure, there is an amazing paucity of accurate data on the physiological effects of hot packs. As has been too often the case with other procedures in physical medicine, conclusions in regard to the effects of hot packs have been based largely upon poorly controlled clinical impressions and observations unsubstantiated by experimental findings.

It is of interest, therefore, that Hall and his associates<sup>12</sup> carried out a well planned study of the strength of muscle contractions after hot woolen packs were applied to the overlying skin of the gastrocnemius muscle of etherized cats. They found that so long as the afferent and sympathetic pathways are intact, the application of hot packs commonly though not invariably, causes slowly developing reduction in the strength of muscle contraction. This effect does not occur when the skin over the muscle is anesthetized. From these experiments the authors suggest that hot packs produce their effects by stimulation of cutaneous receptors which, through some reflex mechanism not entirely clear, reduces the strength of muscular contraction. This result does not occur when reflex effects are excluded.

They observed the greatest decrease in muscle contraction occurred when the subcutaneous temperatures averaged between 46° C. and 48° C. They used deep muscle temperatures as the criteria for blood flow in muscle.

Their conclusion is that hot packs stimulate cutaneous receptors which reflexly evoke vaso-constriction and a reduction in blood flow in the muscles and that this is responsible for the impairment of contraction strength. They go on to state that the present assumption, quite generally accepted, that the application of moist heat "always improves the circulation of the underlying structure" will have to be abandoned if further work confirms their findings that reflex vasoconstriction and consequent decrease in muscular strength can be brought about to a significant degree in human muscles by the application of hot packs. They also suggest that the demonstration of increased mobility of joints and the decreased muscle resistance in stretching following treatment by hot packs may indicate not the removal of the cause of the

muscle hypertonia but weakness of the contracture power of the involved muscle.

It is admittedly dangerous to transfer the results obtained on animal experiments to man. From an anesthetized cat to the child with poliomyelitis is a far cry. Nevertheless, the above mentioned experimental observations are suggestive, although their confirmation must await extensive careful studies on human beings. Should this occur, we may be forced to the conclusion that the results now attributed to hot packs may be brought about by other methods that are less time consuming and costly.

From the foregoing remarks on the effects of heat it may be noted that water in all of its forms and because of its physical properties is frequently employed as the medium for applying thermal stimuli. It seems superfluous, therefore, to discuss the physiological effects of hydrotherapy as such. The effectiveness of most forms of hydrotherapy is dependent largely upon the temperature changes induced. It should be pointed out, however, that some forms of hydrotherapy, especially sprays and douches, combine the effects of mechanical stimulation with those due to alteration of temperature.

There is another physical property of water which has been successfully taken advantage of in physical therapy. When a body is immersed in a liquid there is exerted upon it an upward force which is equal in magnitude to the weight of the liquid which that body has displaced. This law, long ago propounded by Archimedes, is the basis of underwater exercise and manipulation. Since the sustaining power of water almost completely carries the weight of the body, it is possible for weakened muscles and diseased joints to carry out motion under water with little or no discomfort which is virtually impossible to accomplish out of water where the force of gravity must be overcome.

### MECHANO-THERAPY

Under mechano-therapy are included massage, therapeutic manipulation and all kinds of exercise. In spite of careful studies that have been carried out by such investigators as Pemberton,<sup>13</sup> Coulter,<sup>14</sup> Mennell,<sup>15</sup> and others, much remains to be done to bring about a complete understanding of the physiological effects of massage.

Massage differs from active motor stimulation in that the acidosis that occurs with active exercise is not present. Contrary to the effects brought about by the application of external heat, massage does not induce the loss of carbonic and lactic acid with resultant alkalosis. Krogh<sup>16</sup> has demonstrated that the most important effect of massage upon the circulation is the change brought about in the capillary bed. From direct observation on the capillaries it has been shown that massage causes an increased rate of blood flow and changes in the vessel wall which result in an increased interchange of substances between the blood and the tissue cells and consequent improvement in metabolism. The mechanical effect of massage in stimulating the

return flow of venous blood and lymph to the heart is a well recognized phenomenon.

Massage stimulates the contraction of both voluntary and involuntary muscles. Various reflex phenomena result from the stimulation of sensory receptors in the skin as well as in the deeper nerve trunks. With the application of external pressure it is possible to displace the contents of hollow viscera and of accessible glands and their ducts. Collections of inflammatory exudate in skin and muscles may be dissipated by massage. As pointed out by Scull,<sup>17</sup> massage involves the application of the stimulus of pressure to tissues. It has been shown that in normal subjects massage has no significant effect on pulse rate, blood pressure or oxygen consumption.

### THERAPEUTIC EXERCISE

The interest of the physiatrist centers chiefly about corrective exercise, which has been defined as the scientific application of bodily movements in the treatment of disease or malfunction. The subject has attained increasing importance of late because of the prominent rôle which remedial exercise plays in the extensive reconditioning programs now established by various agencies throughout the country. Therapeutic exercise has as its primary purpose not so much the development of muscle power, but rather the acquisition of ability to use muscles effectively in carrying out essential acts and skills.

In spite of the enormous amount of work that has been devoted to the changes incident to muscular contraction, there is still considerable divergence of opinion among competent students of the subject.

Systematic muscular exercise brings about changes in the muscles as well as in the body as a whole. As a result of repeated contractions circulation and chemical activities are stimulated which causes increased muscle size. Exercise brings about hypertrophy of muscle fibers but no increase in their number. This results in gain in muscle power. Systematic exercise is frequently referred to by the term "training." Training not only increases muscle power but facilitates the transmission of nerve impulses across the myo-neural junction, thus allowing more muscle fibers to go into action simultaneously. The precision, endurance and coördination that are developed by systematic training enable an individual to perform movements that require great effort at a minimum energy cost.

An assessment of the working capacity of patients suffering from orthopedic handicaps such as those resulting from poliomyelitis and the mutilations of war and industry is of great practical importance. Steindler<sup>18</sup> investigated the energy cost of walking in patients handicapped from infantile paralysis. Thirteen patients, aged six to 20 years, showed an increase in energy expenditure which ranged from 60.8 per cent to 150.8 per cent above normal. Simons and Keyes<sup>19</sup> compared the energy cost of walking on a treadmill of two subjects who had had poliomyelitis with two nor-

mal controls. One of their subjects was clinically entirely recovered from paralysis. The other suffered almost complete atrophy of the right leg which required braces when walking. In the first case they found that his energy expenditure coincided with normal values in all variations in speed and grade up to 3 m.p.h. with a slight tendency to higher values at 4 m.p.h. The second subject when walking with braces exceeded normal values by 1.5 to 2.6 times in all variations investigated. Without braces this individual's energy expenditure was considerably higher. Respiratory efficiency was definitely lower than that of the patient recovered from paralysis. This work suggests the practical value of evaluating the working capacity of persons with orthopedic handicaps.

The physiological fact that the redevelopment of muscle power, even in markedly atrophied muscles, depends upon high resistive, low repetition exercises led DeLorme<sup>20</sup> to devise a system of heavy resistive exercises. For this purpose he has designed a series of weights which can be attached to various parts of the body so that they can be lifted by voluntary muscular effort. According to his program, one day each week the patient exerts maximal power to lift a suitable weight once. On the other days he lifts a weight which is no heavier than that which is maximum for 10 repetitions. Striking results in improved muscle power have been obtained by this procedure.

Hellebrandt<sup>21</sup> and her associates confirmed an older observation that unilateral heavy resistive exercise not only increases the strength of the exercised limb but brings about a similar concomitant effect on the contralateral unexercised limb. They found that the determining factor in this so-called cross education was the amount of effort expended rather than the duration of the exercise. This cross education may prove a useful therapeutic tool in cases in which voluntary control is unilaterally defective or in which contra-lateral muscle groups are temporarily inaccessible because of immobilization.

It is impossible at this time to do more than point out certain of the physiological effects of the most frequently used procedures in physical therapy. It is hoped that the evidence presented in the foregoing remarks has shown that physical therapy actually is applied physiology. Many basic problems await solution, however, before all of the physiological reactions associated with this broad field of therapeutics are well understood and its procedures satisfactorily standardized.

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# THE USE OF THE ANTICOAGULANTS IN THE TREATMENT OF DISEASES OF THE HEART AND BLOOD VESSELS \*

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## THE TREATMENT AND PROPHYLAXIS OF THROMBOPHLEBITIS AND PULMONARY EMBOLISM

THE first group of diseases to be attacked by means of anticoagulant therapy was quite logically those loosely classified under the broad term of thrombophlebitis, which includes so-called "phlebothrombosis." That this attack has been remarkably successful, though not without some difficulties, is clearly demonstrated by the experiences reported from many workers in this country and abroad.

The significance of this problem is established by the figures compiled by Jorpes from large clinics in widely scattered portions of the world (table 1) (quoted from Zilliacus<sup>1</sup>).

TABLE I

	Cases of Thrombosis	Pulmonary Embolism		Fatal Pul. Embolism	
		Cases	%	Cases	%
	Surgical Cases				
Schneidegg, Singer et al.	1,550	746	48.1	298	19.2
Barker et al.	1,665	897	53.8	343	20.6
Linde et al.	1,230	740	60.1	166	13.5
Obstetrical Cases					
Holzmann et al.	749	119	15.8	26	3.47
Hellsten	420	150	35.8	20	4.76

Courtesy of Dr. J. Erik Jorpes

Thus it is clearly shown that among post-operative patients who develop venous thrombosis and are treated conventionally, there is a minimal risk† approximating 50 per cent, of pulmonary embolization and that among those patients who have one pulmonary embolism, approximately one-fifth will die of a pulmonary embolism. Physicians are just awakening to the gravity of these figures. The profound effect of anticoagulant therapy, using either

\* Presented before the General Sessions of the American College of Physicians, San Francisco, April 23, 1948.

† This is minimal since these figures are based on emboli with infarctions recognized clinically. Autopsy findings indicate that there are large numbers of pulmonary emboli which are never recognized clinically.

heparin or dicumarol, on these statistics has been irrefutably demonstrated by the reports of Allen, Barker and their co-workers<sup>2, 3</sup> (table 2), Zilliacus, Jorpes, Bauer et al. (table 3) of the Scandinavian group, and the previously reported experiences from our own group, and others.<sup>4, 5</sup>

It has also been established that the prophylactic use of anticoagulants post-operatively will decrease the incidence of thrombophlebitis and of pulmonary embolism (table 4).<sup>2, 6, 7</sup>

TABLE II

Effects of Anticoagulants in the Treatment of Postoperative Thromboembolic Complications  
(Barker, Hines, Kvale, Allen)

	Conventional	Therapy Anticoagulant
Thrombophlebitis (352)		
Subsequent		
Thromboembolism	25.3%	2.8%
Fatal embolism	5.7%	0.0%
One Pulmonary Embolism or Infarction (329)		
Subsequent thromboembolism	43.8%	1.0%
Fatal embolism	18.3%	0.3%

TABLE III

Cases of Thrombosis or Pulmonary Infarct  
(Bauer, Zilliacus)

		Death	Per Cent
Conservative treatment	543	88	16
Heparin	769	3	
Dicumarol	131	1	0.45
	900	4	

Courtesy of Dr. J. Erik Jorpes

TABLE IV

Prophylactic Uses of Dicumarol

Allen, E. V., et al., Mayo Clinic	832 Cases Hysterectomy	
Venous thrombosis or Pulmonary embolism	Anticipated with conventional therapy	Occurred with dicumarol
	33	3*
Fatal pul. embolism	6	0
Allen, A. W., and Donaldson, G., Mass. Gen. Hosp.	500 General Surgery	
Fatal pul. embolism	6	0

\* Minor small veins.

## CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

It was natural that following the early encouraging results in the treatment and prophylaxis of thrombophlebitis interested workers would try this approach in other thrombo-embolic syndromes. Beginning in May 1942, therefore, we treated a series of patients suffering from coronary thrombosis with myocardial infarction. Forty-six of these patients were classified as "complicated" in that they had developed either serial episodes of coronary thrombosis, or secondary embolic accidents or both. The first preliminary

report of our experiences with this new approach was presented in this city (San Francisco) in October 1945 before the California Heart Association.<sup>8, 9, 10</sup> Meanwhile others, notably Nichol and Page,<sup>11</sup> and Peters, Guyther, and Brambel<sup>12</sup> had been pursuing the same approach and also published encouraging results. All of these studies were in reality preliminary, exploratory, and they lacked sufficient numbers of cases or adequate control series.

In the summer of 1946, therefore, under the Auspices of the American Heart Association and with the financial support of the U. S. Public Health Service, a study was set up involving some 16 coöperating hospitals well known for their cardiac services. From each of these hospitals a responsible investigator was appointed to the Committee for the Evaluation of the Use of Anticoagulants in the Treatment of Coronary Thrombosis. Each responsible investigator in turn developed his own research team to coöperate with the Central Laboratory Group located in our laboratory at the New York Hospital. Statistical master forms were developed for compilation of data regarding the cases. During the past 20 months patients admitted to the participating cardiac services on even days of the month have received conventional treatment while those admitted on odd days of the month have received conventional plus anticoagulant treatment.

COMMITTEE FOR THE EVALUATION OF ANTICOAGULANTS IN THE TREATMENT  
OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION—  
AMERICAN HEART ASSOCIATION

*Participating Hospital*

Bellevue Hospital, New York  
Beth Israel Hospital, Boston  
Bronx Veterans Hospital  
Cincinnati General Hospital

Cleveland City Hospital  
Henry Ford Hospital, Detroit  
Jackson Memorial Hospital, Miami  
Lakeside Hospital, Cleveland  
Massachusetts General Hospital  
Michael Reese Hospital, Chicago  
Mount Zion Hospital, San Francisco  
Pennsylvania Hospital, Philadelphia  
Peter Bent Brigham Hospital  
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Charles D. Marple, M.D., Coördinator  
Dorothy F. Beck, Ph.D., Statistician

The series has now reached its goal of 1000 alternate cases but because of the necessary lag in statistical analysis, I am able to report to you on the pre-



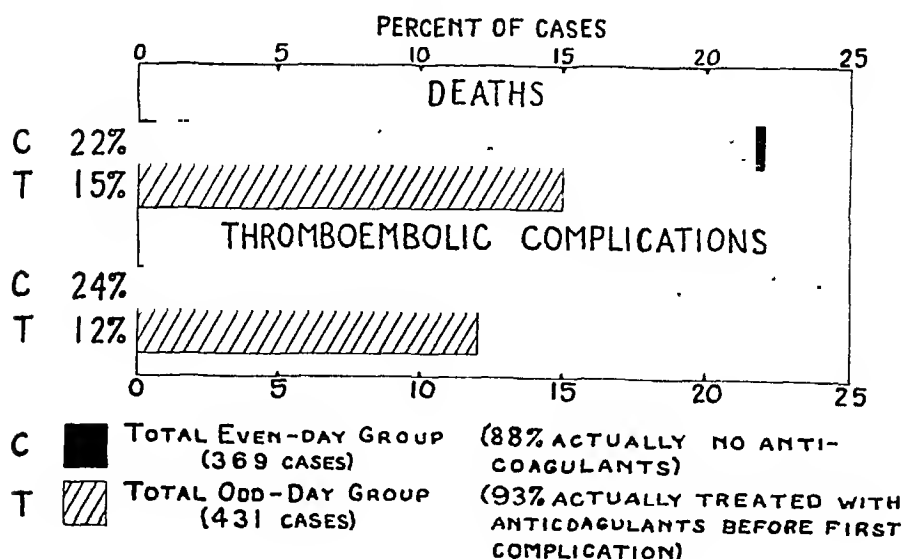


CHART I. Anticoagulants in coronary occlusion with myocardial infarction (800 cases).

liminary crude data derived from only 800 cases. Chart 1 represents the total number of patients classified for statistical purposes as "Even day (control group) patients" and "Odd day (anticoagulant treated) patients." It will be noted that actually 12 per cent of the "Control group" did at some time receive some anticoagulants. This was due to (1) error or (2) pressure from family or other sources after patient had become desperately ill. Seven per cent of the "Treated Group" did not receive anticoagulants before the first complication. This was due to (1) delay in admission, (2) delay in diagnosis, (3) contraindications to use of anticoagulants. Chart 2 offers a comparison of the results obtained with those patients treated solely by means of usual or conventional methods and those who in addition actually received

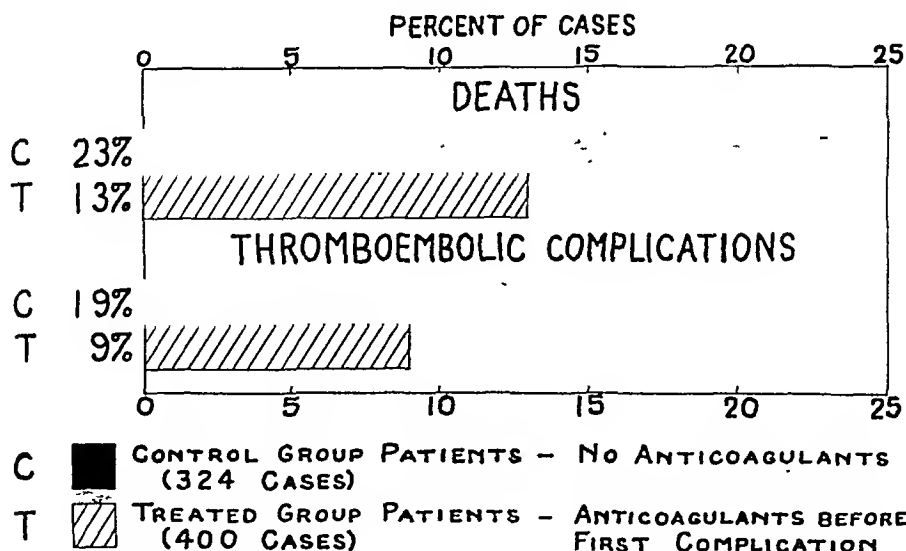


CHART II. Anticoagulants in coronary occlusion with myocardial infarction (800 cases).

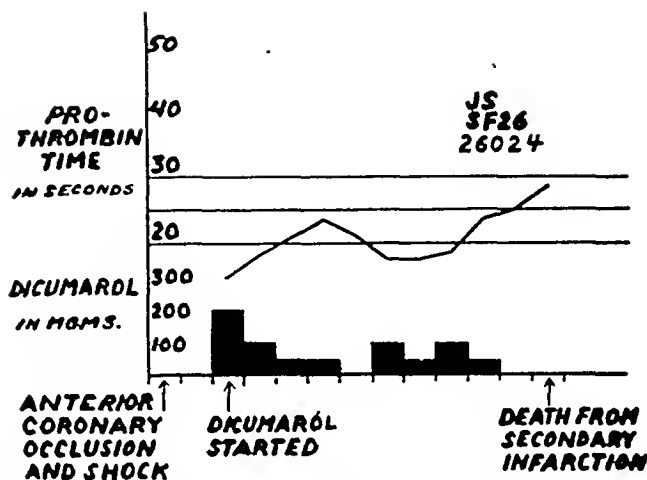


CHART III. Failure with the use of anticoagulant therapy—Note that the therapeutic level of 30 seconds was never reached.

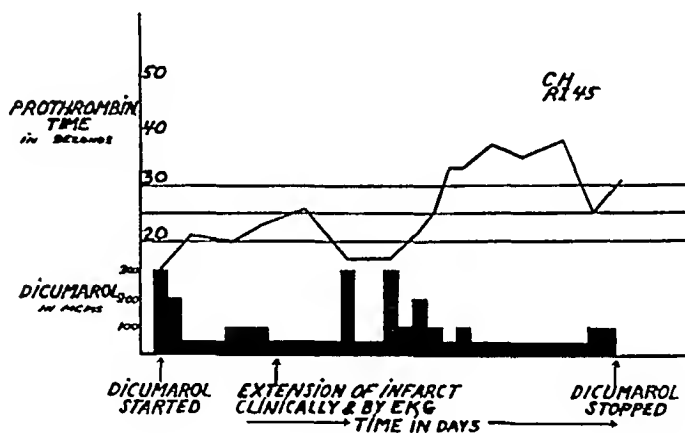


CHART IV. Illustrating inadequate dosage early with a resulting extension of the infarct; later adequate therapeutic levels were attained.

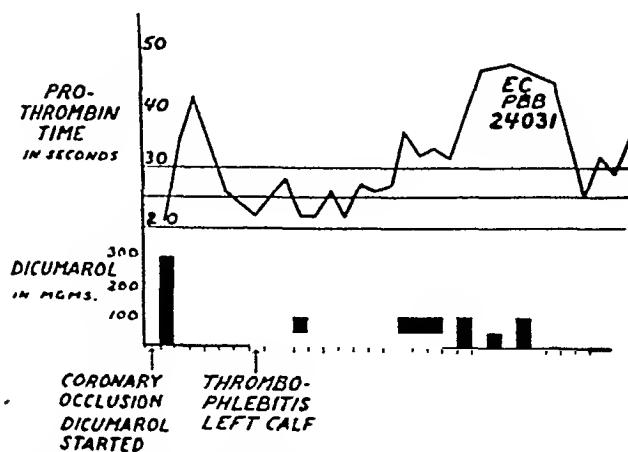


CHART V. A therapeutic level was attained but held for only three days. Three days after the return to subminimal levels thrombophlebitis developed.

anticoagulant therapy. There has been little change in the ratios between the control group and the patients receiving anticoagulant treatment either for deaths or thrombo-embolic phenomena from the statistics on 300 cases upward. The results to date indicate that the incidence of deaths from coronary thrombosis can be reduced from approximately 23 per cent to 13 per cent, or between one-third and one-half, and the incidence of thrombo-embolic complications can be reduced from approximately 19 per cent to 9 per cent, or one-half by the proper use of anticoagulant therapy. This means in reality that by the intelligent use of this new approach one person in three who would be expected to die from a specific attack of coronary occlusion will survive that attack, and that one-half of the anticipated thrombo-embolic complications can be prevented. No attempt can be made at this time to evaluate the effect of this on the factors of longevity and activity of the surviving patients.

*Therapeutic Failures.* The problems of the failures have been the subject of intensive studies by Drs. Marple and Beck of the central laboratory. Charts 3, 4 and 5 illustrate certain factors in this regard. There is a minimal therapeutic level below which anticoagulants fail to achieve satisfactory results. The majority of so-called failures occur because this level is not reached and maintained. For dicumarol therapy this is indicated by the minimal prothrombin time of 30 seconds using a control time of 13 to 15 seconds.\* For heparin therapy, the clotting time should be approximately three times the normal. It is not sufficient, therefore, to state that a patient has received anticoagulant therapy. The key questions which must be answered are: How much? How long? What levels of effectiveness were

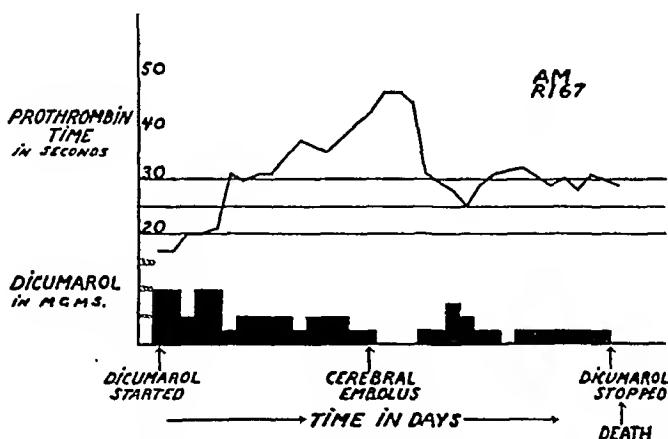


CHART VI. A true failure of dicumarol despite adequate administration.

obtained? How consistently were these maintained? With this information one can determine whether a failure was the responsibility of the drug or of those administering it. Although the majority of the failures brought to our attention have been due to inadequate dosage, a very small number of

\* This equals 30 per cent maximum in our laboratory. In other words, the therapeutic level is between two and three times the normal time.

patients continue to have thrombo-embolic episodes despite apparently adequate dosage of either heparin or dicumarol (chart 6). Some of these have malignancies of the liver, pancreas or elsewhere, others suffer from phlebitis migrans<sup>13</sup> and in some the cause has never been found.

TABLE V  
Hemorrhagic Manifestations

	Total %	Severe %	Moderate %	Mild %	Unknown %
No anticoagulants (322)	3.7	0	0	2.8	0.9
Anticoagulants (409)	11.0	0.2	5.6	5.6	1.0
Anticoagulant only known cause	2.5				
Aggravation of basic cause	1.5				

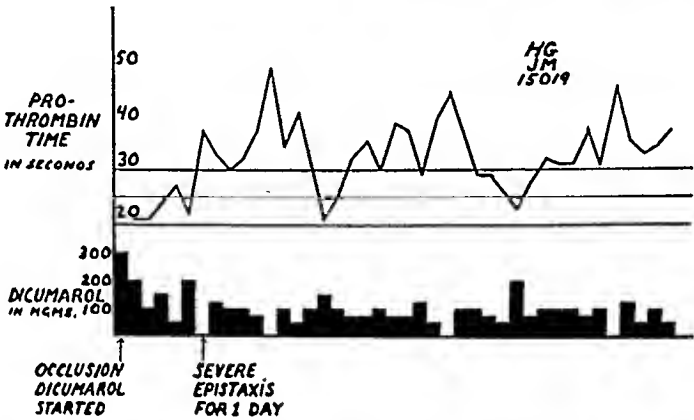


CHART VII. Illustration that all hemorrhages are not directly related to anticoagulant therapy and that if properly evaluated they may not be a contraindication to its use.

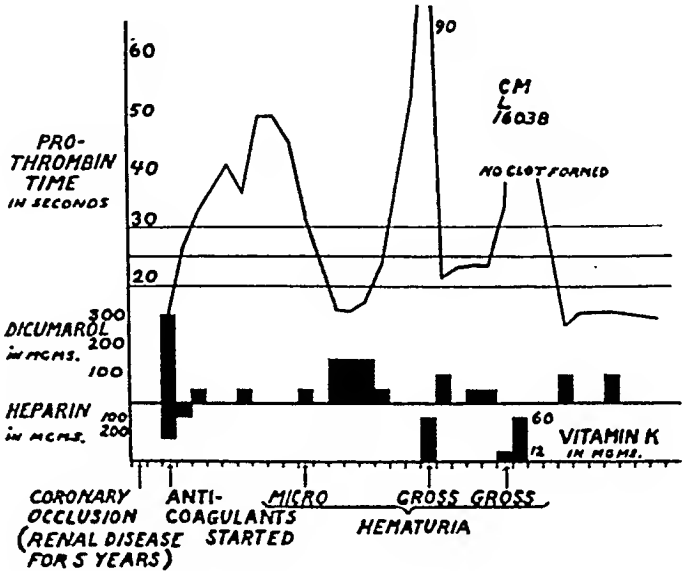


CHART VIII. Demonstrates the difficulties one may encounter in the use of anticoagulants in the presence of renal disease.

*Hemorrhagic Complications.* The occurrence of hemorrhage has also been studied in detail (table 5 and charts 7 and 8). It should be realized that although the incidence of hemorrhagic manifestations is somewhat higher in patients treated with anticoagulants, hemorrhages also occur in patients who have never received anticoagulants (in about 4 per cent of our cases). Serious hemorrhages are rare even among those treated with anticoagulants and are usually due to one of the following factors:

1. Poor prothrombin tests by the laboratory.
2. Lack of sufficiently careful thought and supervision by the physician, resulting in overdosage.
3. The use of anticoagulants in the face of known contraindications.
  - e.g.: (a) Blood dyscrasias
  - (b) Serious liver disease
  - (c) Serious renal disease especially with hematuria or calculi.
  - (d) Gastrointestinal ulceration or colitis.
  - (e) Others.
4. Unrecognized contra-indications such as those above listed, or
  - (a) Unknown peptic ulcer
  - (b) Unknown diverticulitis.
5. Recent surgery or injury—not sufficiently healed.

Animal studies by Blumgart et al.<sup>14</sup> and by Beattie et al.<sup>15</sup> have demonstrated that following ligation of a coronary artery the myocardial infarction area contains no more hemorrhage in dicumarolized animals than in non-dicumarolized animals. This confirms our original observations in man.<sup>9</sup>

The details of the completed study of this new approach to the treatment of coronary thrombosis with myocardial infarction will be presented at later meetings this year and will be published.

#### RHEUMATIC HEART DISEASE WITH AURICULAR FIBRILLATION AND MULTIPLE EMBOLIZATION

The next patients to stimulate our interest were those who were suffering with old rheumatic heart disease, with auricular fibrillation, and who then developed intra-cardiac thrombi, from which multiple emboli were repeatedly cast off. These have previously represented among the most discouraging problems in medicine since neither the patient nor the doctor could predict when an embolus would cause the loss of an extremity, paralysis, or death. The former treatment has been largely fatalistic, accompanied by attempts to keep the heart in a state of compensation but with no assurance that this would prevent embolization.

The treatment of these cases was begun in the late summer of 1946, and reports of our results have been published.<sup>13, 5, 16</sup> To date 22 such patients have been treated first in the hospital and later on a permanent ambulatory

basis. As reported, patients who have had as many as 12 and even 20 emboli have ceased having emboli and in the six treated more than one year (one 19 months) no emboli have occurred. Difficulty in arranging to keep patients on long term ambulant anticoagulant therapy has produced problems and emboli have occurred in several individuals who have not been faithful to the regime, but it is apparent that ambulant long term dicumarol therapy is a distinct advance in the treatment of this extremely serious condition—though it is not an infallible one and it is a difficult regime for the patient and the doctor to follow indefinitely.

### LONG TERM AMBULATORY ANTICOAGULANT THERAPY

Experience with anticoagulants, especially dicumarol, in long term ambulatory treatment has been studied by Nichol and Fassett,<sup>17</sup> and by Foley and the author.<sup>18</sup> Certain of Nichol's cases have now been on dicumarol therapy for three and four years. We are reporting one series of 19 patients who have been on continuous dicumarol therapy for an average of nine months—the longest, for 18 months. The conditions for which such an approach seems advisable at present include:

1. Rheumatic heart disease with fibrillation and multiple embolic episodes.
2. Phlebitis migrans—persistent.
3. Recurrent thrombophlebitis including familial thrombo-embolic disease.
4. Recurrent coronary thrombosis with myocardial infarction.

This technic is fraught with inherent difficulties centering about the need for frequent (once or twice weekly) accurate prothrombin tests, close medical supervision, and intelligent coöperation on the part of the patient. The problems encountered and how they have been met are discussed in detail in the papers above referred to.

It has been demonstrated by laboratory tests and autopsy findings that prolonged treatment with dicumarol in clinical dosage does not result in damage to the kidneys or to the liver.

### THE COMBINED USE OF ANTICOAGULANTS AND QUINIDINE

Recently, interest has been refocused on the possibility of reducing the risk of embolization following the administration of quinidine for the restoration of normal rhythm in patients with auricular fibrillation. Saland<sup>18</sup> and his co-workers and others have had a considerable experience in this field. We have used it to some degree. There are numerous questions which arise regarding this controversial subject. Chief among these are: Is there an advantage in the conversion of a fibrillating heart to normal rhythm? Which cases should be selected for this approach? Will such a heart maintain regular rhythm sufficiently long to warrant any risk of conversion attempts? Does the use of quinidine actually increase the risk of emboliza-

tion? These questions have been the subject of numerous but not completely conclusive studies in the past. No attempt will be made to analyze them here or to evaluate the rôle of anticoagulants in this regard. The question is at present reopened for further investigation.

### A REVIEW OF THE PAST AND THE CHALLENGE OF THE FUTURE

It now appears that the story of the use of anticoagulants in thrombo-embolic diseases will be a long and rewarding one. Only the first chapters have been written. These include:

1. The identification and production of heparin and dicumarol.
2. The demonstration that they inhibit clotting processes in vitro and in animals.
3. The establishment of their practical application and therapeutic usefulness in man.

Despite their great value in establishing the importance of this type of therapeutic approach, it is well known that neither heparin nor dicumarol is a completely satisfactory anticoagulant. The advantages and disadvantages of each have been adequately stressed in the literature and will not be repeated here.

It is essential for the full development of this form of therapy that future chapters include the production of new, improved anticoagulants and simpler methods for the control of their administration.

The following requirements should be fulfilled by the ideal anticoagulant:

1. It should be therapeutically active when administered orally or parenterally—without producing digestive or hypersensitivity reactions.
2. Its action should be rapid, affecting the clotting tendencies of the blood within one hour.
3. The dosage should be easily standardized and fairly uniform for a given patient and as between different patients. The action should be predictable in terms of quantitative response.
4. It should be relatively non-toxic with a wide safety zone between therapeutic effect and toxic damage to important organs. It is obvious that there will always be some hazard from bleeding essential to the very nature of this therapeutic approach. This should not be regarded as a toxic effect but rather as an overextension of the therapeutic effect of the drug.
5. The action of the drug should be promptly terminated after stopping its administration or following the use of an effective antagonistic agent which in itself is free from undesirable effects.
6. A test for the activity of this substance should be sufficiently simple to permit its control by the family physician or, even better, by the patient.
7. The anticoagulant should be inexpensive.

The development of such a drug would greatly broaden the application of anticoagulant therapy. The fact that an extremely high percentage of persons in the older age groups die or are crippled by thrombotic episodes raises interesting questions regarding the widespread prophylactic use of such a drug, as first suggested by E. V. Allen.

### SUMMARY AND CONCLUSIONS

1. The value of the anticoagulants dicumarol and heparin in the treatment of thrombophlebitis has been conclusively established.

2. The importance of the use of anticoagulants post-operatively in the prophylaxis of thrombo-embolic complications has been clearly demonstrated.

3. Data based on extensive studies indicate that the death rate from coronary thrombosis with myocardial infarction can be reduced one-third and the incidence of thrombo-embolic complications can be reduced one-half by the use of anticoagulants.

4. The majority of therapeutic failures to date have been the result of inadequate anticoagulant treatment. Some failures occur in spite of apparently adequate therapy.

5. Hemorrhagic complications occur in patients who have never received anticoagulants but are more frequent in those who have. These problems have been discussed.

6. The value of anticoagulants in the prophylaxis and treatment of the thrombo-embolic complications of auricular fibrillation appears significant.

7. The indications for long term ambulatory treatment with anticoagulants have been presented.

8. The question of conversion of auricular fibrillation to normal rhythm with quinidine, and the possible value of anticoagulants in this technic has been briefly presented.

9. The needs for and the requirements which should be fulfilled by an ideal anticoagulant have been outlined.

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# CERTAIN CLINICAL ASPECTS OF THE APPLICATION OF WATER BALANCE PRINCIPLES TO HEART AND KIDNEY DISEASE\*

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DURING the past 15 years, my colleagues and I have been applying true water balance principles, with a proper regard for sodium and acid-base balance, to all our seriously ill patients. We have done this in all departments, surgery, obstetrics, pediatrics and medicine, for the prevention or correction of oliguria or anuria and azotemia, and of dehydration and edema. We have found this practice to be of value in the prevention of serious renal complications in general. We believe that, particularly in cardiovascular-renal disease where such complications are so frequently encountered, it has reduced our morbidity and mortality.

At the annual meeting of this college, six years ago, we stressed the observations we had made on patients with cardiac disease and edema.<sup>1</sup> This was done because of the common practice of restricting fluids in the presence of edema, especially in patients with heart disease. As Sir Francis Milman<sup>2</sup> put it, "lest futile and exploded theories be set against facts and experience." we cited some 400 observations which have grown to number over 1000. We saw, as he did in 1786, that "to irritate the body with medicines and prohibit drink is prejudicial to the patient and that treatment will be much more fortunate with large and frequent draughts of diluting drinks."

In our 1942 report we said that "a daily intake of 2500 to 3000 c.c. was adequate for the majority of cases." However, we did also confirm what Austin Flint<sup>3</sup> had said, "*that more than enough water is not too much.*" For, in order to establish the point that it was safe to give whatever amounts of plain water might be dictated by water balance principles in the more seriously ill, "we often carried our intakes *higher than optimum* and repeatedly observed the rapid clearing of massive edema in the face of intakes averaging 6000, 7000, or 8000 c.c. daily."

In this paper we shall stress the water requirements in *renal disease* and in the renal complications of cardiac disease. For while renal function disturbances greatly increase the requirements of the body for water, there appears at this time to be such preoccupation with the protein and sodium requirements in renal disease that the water requirements are often ignored or disastrously underestimated.<sup>4, 15, 16</sup>

This may be because, as the President of the Medical College of Paris<sup>5</sup> suggested in 1721 in commenting on its virtues, "water is too common, too

\* Presented before the meeting of the American College of Physicians, San Francisco, April 20, 1948.

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much known, and, therefore, too little esteemed." More probably it is due to failure to appreciate the full significance of the work on renal function and insensible water loss done by Newburgh<sup>6, 7, 8</sup> about 20 years ago on the basis of which he was able to give quantitative expression to the water needs of the body. Coller<sup>9, 10, 11</sup> realized the significance of the work and extended it so effectively to the reduction of surgical morbidity and mortality that death in a brine-logged condition or from so-called postoperative nephritis is now more of a reproach than an alibi to a surgeon.

It is obvious that man's need for water is secondary only to his need for oxygen. Yet, in health, he maintains water equilibrium with an intake of only about one quart of water as such, plus one quart of water derived from his solid food, which is balanced by the loss by evaporation of about a quart of water from the lungs and skin for temperature regulation and about a quart of water eliminated as urine water to carry off the solids which demand excretion.\* One of the most common manifestations of disease is the breakdown of this economical use of water.

In the past, we thought that three liters of water were more than enough for a sick person and that his development of anuria or edema was due to the inability of the kidneys to excrete water or salts. Studies in the last two decades, particularly of water metabolism and renal function, however, show that:

(1) Even badly impaired kidneys *can* excrete all the plain water that reaches them and can excrete the sodium and metabolic solids which reach them if enough water reaches the kidneys to provide them with from 2000 to 3000 c.c. of urine-water daily.

(2) The vaporization of water for temperature regulation in disease may demand as much as 2000 to 5000 c.c. of water before any can reach the kidneys.

(3) A preëxisting true dehydration, or plain water deficit, which is often encountered in the presence of edema as well as in its absence, may require for its correction from 4000 to 7000 c.c. of water before any reaches the kidneys.

(4) Retention of sodium salts, along with an excess of basic ash sufficient to neutralize the metabolic acids, results in the diversion of water to edema formation in amounts that might otherwise be adequate for the needs of the body.

(5) Extra acid sodium salts and nitrogenous wastes, in the presence of an insufficient supply of water, are eliminated in urine water derived from the expendable fraction (4000 to 7000 c.c.) of the 50 liters of body water, almost three-quarters of this water coming from the cells. The resultant cell dehydration seems to be more harmful to the cells of the body than either edema or azotemia.

\* For simplification, the 200 c.c.  $\pm$  of water of stool is considered to be balanced by pre-formed water or water of oxidation.

These facts show, to cite a quite ordinary example, that a patient, with a true dehydration from a previously inadequate intake, and with a fever, and a low fixed specific gravity, might require a total of 4000 c.c. for body water deficit replacement in the first day or two, and in addition might require 2000 c.c. daily for vapor loss, before any water could reach the kidneys. The kidneys themselves would then require 2000 c.c. daily of urine water to carry away the daily solids. Such a patient could be restored to normal balance only by giving 6000 c.c. daily for two days and 4000 c.c. daily thereafter, and not then unless unnecessary amounts of sodium or protein were avoided to prevent a diversion of water from the kidneys or an increase in total urinary solids. An intake of 3000 c.c. daily for this patient would merely increase his plain water deficit each day; and dehydration, anuria and azotemia could neither be prevented nor corrected.

Young people with normal kidneys who are deprived of only 4.5 liters of plain body water develop severe oliguria, a moderate retention of urea and salts, and evidence of renal injury in the form of albuminuria, casts and red cells.<sup>9</sup> The plain water deficit in the very ill often amounts to from 4.5 to 7 liters. Such a deficit results in a degree of cellular dehydration and of extracellular fluid concentration (true dehydration)<sup>12</sup> which is capable of injuring *normal* kidneys or of making *diseased kidneys* worse, or of precipitating a so-called "renal shut-down." The resistant anuria which results and is occasionally irreversible, is usually attributed entirely to the *inability* of the kidneys to excrete water or salt.<sup>4</sup> Actually, it appears that short of ligation of the ureters and the virtual suspension of cell function in truly terminal stages of disease, anuria and edema result in the vast majority of instances from exhaustion of body water and from the diversion of water (and salt) from the kidneys, and not from inability of the kidneys to excrete water and salt. Our observations show that this concept holds up well in practice. It can be applied by the estimation of water and sodium needs from relatively simple data, and by the satisfaction of these needs with the clinical and therapeutic technics described in our 1942 report.<sup>1</sup>

Other facts from these studies and from clinical experience should be emphasized:

(1) Not less than the estimated amounts of water should be given; if possible by mouth, but if necessary *without hesitation* by vein.<sup>13, 14</sup> The water of 1000 c.c. of an isotonic solution of dextrose in distilled water is swiftly diffused throughout all 50 liters of the body water; while a similar volume of isotonic sodium chloride is distributed rapidly but throughout only 14 liters of extracellular fluid; blood and plasma volumes are added to about 6 liters of circulating blood.

(2) With rehydration and a large volume of urine water, mercurial diuretics can be used safely in nephritis and often with great benefit, whereas with an inadequate water supply they may induce evidence of renal injury in patients with originally normal kidneys. In the most resistant cases

however, a good output of urine water, with an adequate restriction of sodium and the use of mercurials, may be ineffective in clearing edema until enough acid is supplied to augment the action of the metabolic acids and "mobilize" sodium.

(3) Serious loss of salt, plus water, may occur in the course of treatment of edema with acid and mercurial diuretics and extremely low sodium diets, as well as from vomiting, diarrhea or profuse diaphoresis. But *brine* is not *water*, and the replacement of body fluid loss and the correction of acute disturbances of electrolyte pattern with *saline* solutions should be accompanied by the simultaneous maintenance of a true water balance with *plain water*.

(4) In acute deficits of sodium or protein small amounts of either will promptly correct the deficit. But in advanced chronic disease, the low carbon dioxide combining power and low serum proteins are only transiently affected or affected not at all, by large amounts of sodium or protein, which may harmfully divert water from the kidneys and increase the amount of solids (nitrogenous wastes and sodium salts) to be excreted by the kidneys.

Many cases of advanced nephritis are relatively asymptomatic and quite active with a carbon dioxide combining power of around 20 volumes per cent, a level which appears to be dictated by the functional state of the kidney rather than by lack or loss of sodium. In these cases small amounts of acid drugs do not disturb the sodium level and can be safely used, only, however, with an adequate amount of urine water.

The level of the serum proteins in chronic nephrotic syndromes is similarly determined by the level of impairment of the synthesis and exchange of protein and not by lack or loss of protein. Edema which has resisted high protein diets and as much as 75 grams of sodium-free human albumin daily can be cleared with the ingestion of only 40 grams of protein daily and the proper manipulation of water and sodium. If synthesis and exchange are improved, the serum proteins are even seen to rise on this 40 gram protein intake.

We have outlined a few of the facts and experiences which explain our therapy.<sup>1</sup> These have led us, for example, to avoid the use of sodium salts with sulfonamides for they often divert so much water from the kidneys that, in spite of an alkaline urine, oliguria and crystallization develop, while the latter do not develop when a large volume of dilute *acid* urine is maintained. The crystallization of sulfonamides in the tubules and anuria can be corrected without recourse to decapsulation of the kidneys: thus, one of our patients received 16 liters of water in 36 hours to break successfully an absolute anuria that had persisted for 42 hours.

Data in reports on cases submitted to decapsulation of the kidneys and, more recently, on those submitted to peritoneal or intestinal lavage suggest that the development of what are considered the indications for these procedures might have been prevented or the results of lavage improved, had the same pains been taken to maintain true and adequate water balance as

were taken in maintaining sodium and protein balance.<sup>15, 16, 17</sup> Thus in one such report,<sup>18</sup> a patient with renal injury and moderate fever showed a progressing oliguria and azotemia which culminated in complete anuria by the eighth day, when he was submitted to peritoneal lavage. The data show that in the eight days before operation he received what were considered to be proper amounts of R-molar lactate and protein which yielded coincidentally a total of 56 grams, or 7 grams daily, of sodium salts, while in these eight days he had received only 1800 c.c. of water daily. This amount of water could not correct any antecedent water deficit and was scarcely enough to provide for the demands of vaporization alone. The development of complete anuria was, therefore, inevitable. The greatest recorded intake of water in the other case reports was an average of 3000 c.c. daily.<sup>17</sup>

The following briefly outlined cases from our series illustrate our observations and practice in patients with oliguria or anuria, and azotemia and edema in cardiac or renal disease: \*

Cases given an adequate amount of water to correct a severe preëxisting dehydration commonly follow the pattern illustrated by R. W. S. during the time in which their water deficit is being made up.

This patient was admitted five days after an acute myocardial infarction with edema and Adams-Stokes convulsions. Urine, heavy with albumin, was obtained by catheter six hours after admission in the amount of 125 c.c., to end an anuria of 20 hours' duration. In the first 24 hours almost all of the 5000 c.c. of water received was taken up by thirsty cells or vaporized so that only 775 c.c. of water reached the kidneys to form urine. There was the usual slight increase in edema, but with this, as is often seen, there was a marked general improvement as evidenced by clearing of the sensorium and, in this case, the cessation of convulsions, well before diuresis began. In the next 14 hours, 4100 c.c. of urine water were elaborated (intake 3500 c.c.), and the blood urea dropped from 75 to 23 mg. and the edema began to clear.

An example of the free use of intravenous solutions in a patient with severe injury of the myocardium and so-called renal shut-down is presented in the patient. E. P. He was admitted five days after a posterior infarction with a blood urea of 196 mg. An anuria of 42 hours' duration was overcome only after 10 liters of water had been received; the urine obtained was bloody. His average daily intake of 5000 c.c., which was largely dissipated by fever and diaphoresis, was attained with from 2000 to 3000 c.c. daily of isotonic dextrose by vein. In spite of this intake, his relative oliguria and his edema persisted until the fourteenth day, when following a drop in his temperature, which lessened his vaporization demands, diuresis began and the clearing of edema and azotemia was rapid.

Our practice in the replacement of salt and water loss (loss of extracellular fluid, commonly referred to as dehydration) is illustrated by A. V. F.

\* Much fuller data on some of these cases and many others are presented in Part II of the 1942 report.<sup>1</sup>

who was seen in extreme shock with marked hypochloremia and oliguria following a period of vomiting and diarrhea. In five days she tolerated 30 liters of water with 80 grams of salt, the equivalent of 9 liters of isotonic sodium chloride plus 21 liters of plain water, a ratio of 1 to 2, which is about the lowest ratio of brine to water that we use. The 20 liters of plain water provided for vaporization loss and an adequate amount of urine water, and did not hinder correction of the hypochloremia and restoration of volume of the extracellular fluid. She responded rapidly and edema was not produced although she was fibrillating, had both mitral stenosis and aortic insufficiency, and had been edematous four days before admission.

An example of our management of cases with chronic glomerular-nephritis with nephrotic features and cardiopathy, and with low serum proteins with a low serum albumin is seen in F. G. In an earlier hospital admission elsewhere it had been felt necessary to restrict fluids, give a high protein diet, and augment the osmotic pressure of the blood with acacia in order to clear his edema. A year later, we were able to clear his edema in eight days on an average daily intake of 5000 c.c. with a "neutral" diet yielding only 40 grams of protein. The serum protein and serum albumin remained at about 4 and 2 grams per cent respectively; later a diet protein of 120 grams did not increase these levels. As his disease progressed a carbon dioxide combining power of 20 to 30 volumes per cent permitted moderate activity, and extra sodium as R-molar lactate only produced thirst and edema without producing more than a slight transient effect on the carbon dioxide combining power level.

Our practice in acute fulminating hemorrhagic nephritis with scanty, bloody urine or anuria is indicated by M. S. who was admitted in coma after two convulsions. All of her intake, for the first six and one-half days before her coma was relieved, was by vein and averaged 4000 c.c. daily. The sodium received in 1500 c.c. of blood and plasma about equalled that lost in approximately 3000 c.c. of emesis and stool. In spite of 9500 c.c. of water in the first 56 hours the oliguria became worse until only a few c.c. of bloody urine per hour were being elaborated. In the next 28 hours, however, when attention was directed to the mobilization of sodium by acidification and 10.5 grams of ammonium chloride were given along with 5000 c.c. of water by vein the renal shut-down was overcome and 4000 c.c. of urine were elaborated. For the next eight days an average output of urine of 2500 c.c. daily was maintained and there was steady clinical improvement, in spite of a drop in the carbon dioxide combining power from 52 to 33 volumes per cent and without either clearing of edema or actual diuresis. In the next seven days edema cleared, while the carbon dioxide combining power rose, on a low sodium, 40 gram protein diet. She was maintained on this diet until there was no evidence of residual nephritis and renal function tests were normal.

## COMMENT

Although Newburgh summarized his studies on *The Importance of Dealing Quantitatively with Water in the Study of Disease* in 1933, there is evidence in the current literature<sup>4, 15, 16, 17</sup> of a lag in the application of these principles to problems in internal medicine. This is disturbing, for it is well known that what Sir James MacKenzie called a "true scent" in medicine may be lost and buried for generations.

As long ago as 1706, a Fellow of the Royal College of Physicians<sup>5</sup> was on such a "true scent." He speaks of insensible perspiration and regards retained salts as responsible for thirst. He finds that the urine from a sick man contained "but the thirtieth part of those salts usually found in a sound man's urine so that, of necessity, salts must remain behind and be left like so many French Dragoons to quarter on the blood and fluids at discretion." He remarks that "These salts creep with the chyle into the blood and have no way out but by the urine, and that for dissolving these salts, that water is best which has least content." Here, buried for over 200 years, is awareness on a qualitative basis of the effect of an undue accumulation of salts in the body, and of the need of the body for plain water for vaporization purposes, for the uses of the kidneys, and for the correction of true dehydration.

The importance of these requirements of the body for water in serious illness should not be lost sight of in our preoccupation with the requirements of the body for protein and sodium, which, although very important, do not lessen and often themselves increase the need of the body for plain water.

## CONCLUSION

In applying water balance principles in renal disease and in the renal complications of cardiac disease for the correction or prevention of anuria, azotemia and edema we have found it especially important to keep in mind:

1. That the increase in the plain-water needs of the body in serious illness is often of great magnitude.

2. That water does not reach the kidneys until all the other demands of the body for water have been satisfied, and

3. That brine is not water. The sodium laden water of Ringer's, R-molar lactate and Tyrode's solutions, and of ordinary plasma and of blood, as well as the water of isotonic sodium chloride solutions, should not be counted in the plain-water intake, because their water cannot be satisfactorily used for the metabolic purposes of plain-water.

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# CLINICAL OBSERVATIONS WITH FAGARINE\*

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ALTHOUGH there has been considerable progress in therapy recently, new remedies for the treatment of cardiac arrhythmias deserve attention. Any one who has seen a patient die as the result of persistently rapid heart rate in a paroxysmal tachycardia, refractory to digitalis, quinidine, and other drugs even in large doses, will welcome a new therapeutic agent.

Alpha-fagarine hydrochloride,† an alkaloid extracted from the Argentinean plant *Fagara coco*, has been recommended for certain disturbances of stimulus formation.<sup>1</sup> It has been used in man,<sup>10, 11</sup> and available reports suggested that further studies of the drug were justified.

## METHOD

During the clinical use of fagarine in a small series of cases, arrhythmias in form of multifocal ventricular extrasystoles were observed<sup>10</sup>; we decided, therefore, to use this drug mainly in hopelessly ill patients suffering from advanced cerebral arteriosclerosis, metastatic carcinoma, uremia, etc. Many of the patients were over 70 years old. Not only did they present a cardiac lesion, usually in the form of coronary sclerosis with auricular fibrillation, but their systemic condition and debility could not help but influence their cardiac status.

Fagarine was injected intramuscularly in an amount of less than 2 mg. per kilogram when the weight could be determined. The weight of the patient was estimated when conditions precluded actual weighing.

Lead II of the electrocardiogram was obtained before the injection and every five to 15 minutes following the injection for two hours or longer. Whenever observation of the string showed a change in cardiac activity, the electrocardiogram was immediately registered.

The blood pressure was also determined every 10 or 15 minutes and the patient was constantly observed for appearance of untoward signs.

## RESULTS

*Case 1.* P. M., an 86 year old white female, had suddenly become paralyzed and lost the power of speech. There had been a cerebrovascular accident 36 years previously with some residual aphasia and right hemiparesis. According to the information obtained from the family physician, auricular fibrillation had been continuous for a long time with moderate hypertension. On admission, the blood pressure was

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160/100 mm. Hg. The heart was enlarged to the left and auricular fibrillation was present. A systolic aortic murmur was audible. There was a right hemiplegia. Little change was noted in her condition on a regime of physiotherapy and digitalis in the amount of 0.1 gram per day.

Digitalis was discontinued one week before fagarine was given. The dose of the latter amounted to 0.06 gram by intramuscular injection. The blood pressure over a two hour period showed a gradual decline from 150/90 to 134/74 mm. Hg with essentially no change in the condition of the patient. The electrocardiogram showed no change, but next morning normal sinus rhythm was found for the first time.

Two days later, the patient had sudden lower left chest pain; she became cold and clammy and developed pulmonary edema. She died on the fourth day after the injection. Another electrocardiogram taken just prior to death revealed the persistence of the sinus rhythm.

Postmortem examination revealed coronary sclerosis, myocardial degenerative changes, old posterior wall infarction, aortic atheromatosis, and left lower lobe bronchopneumonia. The cause of death was ascribed to a new posterior wall infarction.

*Summary:* An 86 year old woman with repeated cerebral accidents, hypertension and auricular fibrillation received an injection of 0.06 gram of fagarine. This was not followed by any change in the electrocardiogram or in the condition of the patient during an observation period of two hours. Sinus rhythm supervened, however, within the next 12 hours and persisted until death.

*Case 2.* A. M., an 87 year old white male, was admitted for an attack of syncope. He was disoriented and presented a picture of dehydration, malnutrition, and cerebral arteriosclerosis. There had been a sudden onset of loss of speech one year previously without paralysis followed by some improvement. The heart was slightly enlarged and showed a rapid, irregular ventricular rate. The electrocardiogram on admission showed auricular flutter with varying 2:1 and 4:1 block. During the administration of digitalis, the flutter temporarily stopped but recurred and persisted.

On the twenty-second day in the hospital, 0.06 gram of fagarine was injected intramuscularly but the electrocardiogram taken at the time of the injection showed that the patient had spontaneously developed normal sinus rhythm. There was neither subjective nor objective evidence of a disturbance ascribable to the fagarine. No significant changes of the blood pressure were observed.

Figure 1 shows the form of the RS-T segment and the T-waves before, and 30, 50 and 90 minutes after the injection. There was a very slight depression of the RS-T segments and no change in the form of the T-waves. The P-R interval measured 0.24 second before and after the injection and throughout the period of observation.

*Summary:* The injection of 0.06 gram of fagarine in an 87 year old patient was followed by no untoward symptoms. The electrocardiogram showed only slight changes. Sinus rhythm was present at the time of the injection.

*Case 3.* R. M., a 65 year old woman, was admitted with a history of chills and fever for one day. A number of years previously she had been told that her blood pressure was high and she knew that diabetes mellitus existed three months prior to this admission; auricular fibrillation had also been discovered at another hospital.

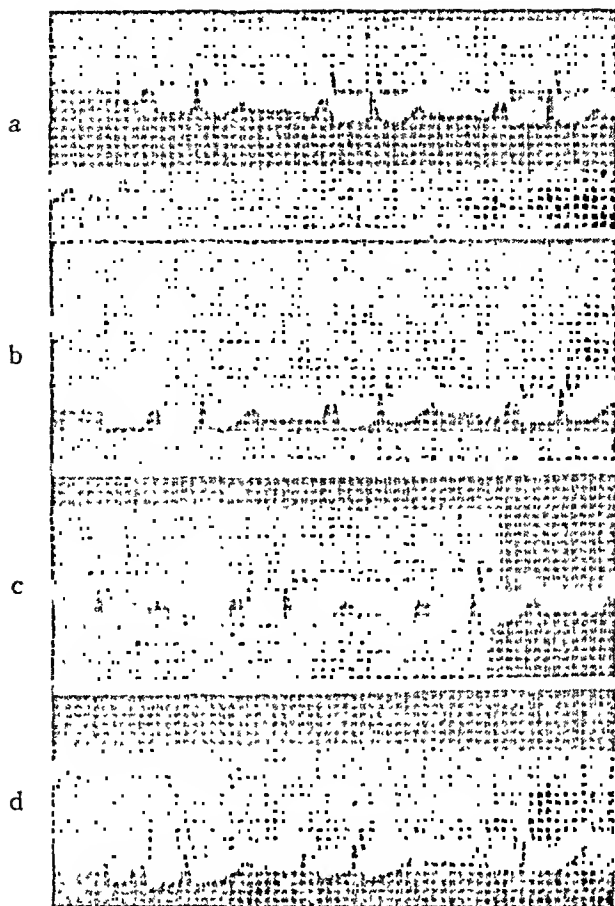


FIG. 1. The top tracing shows Lead II before the injection of 0.06 gram of fagarine; the other tracings represent Lead II taken at intervals of 30, 50 and 90 minutes respectively after the injection (case 2).

On admission, the patient was confused, uncoöperative, dyspneic and cyanotic. There was evidence of left lower lobe pneumonia with a temperature of  $40^{\circ}$  C. The heart was enlarged to the left and the pulse was irregular with a ventricular rate of 128. There was an apical systolic murmur. The blood pressure was 120/60 mm. Hg. The pneumonia resolved during two weeks of penicillin therapy and the diabetes was controlled with 20 units of protamin-zinc insulin. The cardiac rate continued to be irregular but went down to 100 without administration of digitalis.

The patient received 0.09 gram of fagarine intramuscularly. Fifteen minutes later she complained of buzzing in the ears. This diminished after 30 minutes and disappeared after two hours. During the observation period of two hours and 15 minutes, the blood pressure varied from 132/70 to 150/90 mm. Hg.

The electrocardiogram showed auricular fibrillation with left axis deviation before the injection. There was no change during the observation period of two hours after the injection. The auricular fibrillation persisted and the QRS complexes as well as the T-waves showed no variation.

*Summary:* In a 65 year old woman with auricular fibrillation, diabetes and pneumonia, the injection of 0.09 gram of fagarine produced no electrocardiographic effect.

*Case 4.* C. G., a 68 year old white male, was admitted with the history of a right hemiplegia which occurred on the previous day. Hypertension had existed for at least five years; the patient had suffered from a right hemiplegia four years prior to admission with complete recovery. Physical examination revealed Cheyne-Stokes respiration, a flaccid paralysis of the right side and motor aphasia. The cardiac rate was very rapid and totally irregular because of auricular fibrillation. Apical and aortic systolic murmurs were present. The blood pressure was 240/128 mm. Hg.

The electrocardiogram (figure 2) showed auricular fibrillation with rapid ventricular rate. There was marked left axis deviation with a left ventricular strain pattern; the QRS complexes were plump and slurred but only 0.10 second wide. The RS-T segments were depressed in Lead I and showed a convexity directed upward. They were followed by deeply inverted T-waves. The opposite direction of QRS segments and T-waves was also visible in Lead III. The chest leads indicated left ventricular hypertrophy.

Before any digitalis was administered, 0.12 gram of fagarine was injected into the gluteal muscles. The blood pressure at that time was 230/100 mm. Hg. New determinations were made at 10 minute intervals for one hour, and at 15 minute intervals for the second hour. The variations did not exceed 20 mm. Hg in the systolic pressure or 20 mm. upward in the diastolic pressure. There were no untoward symptoms after the injection.

Five minutes after the injection, there were no changes in the electrocardiogram but 10 minutes after the injection the auricular fibrillation changed into auricular flutter and a series of ventricular extrasystoles originating in one focus occurred (figure 3a). Fifteen minutes after the injection (figure 3b), the auricular flutter had disappeared and sinus rhythm with marked disturbances of stimulus formation in the sinus node was present. The P-waves were variform. The length of the P-R interval varied and premature blocked P-waves were visible. Ventricular extrasystoles still persisted. This picture remained without change although the disturbances were even more pronounced 70 minutes after injection (figure 3c). Gradually, the number of normal sinus impulses increased and extrasystoles diminished. Three hours after the injection, regular sinus rhythm was registered (figure 3d). Sinus rhythm persisted and was present when the patient was discharged 10 days later.

*Summary:* In a 68 year old man with hypertension, old and recent hemiplegia, and auricular fibrillation, 0.12 gram fagarine caused auricular flutter within 10 minutes. Sinus rhythm appeared in 15 minutes with marked disturbances of stimulus formation and conduction. There were no other untoward effects.

*Case 5.* M. Y., a 45 year old white female, was admitted because of cold sweats, insomnia, palpitation, and nervousness of five days' duration. For 22 years she had had recurrent episodes with similar complaints, of sudden onset and sudden termination with increasing frequency lasting from a few days to a few hours. On admission, she was moderately dyspneic, pale, with slight cyanosis of the lips. The heart rate was 160 and the rhythm was regular. The heart sounds were of equal intensity (embryocardia).

Paroxysmal tachycardia of supraventricular origin (figure 4a) with a rate of 200 was found in the electrocardiogram and the patient was given 0.1 gram of fagarine. There were no symptoms referable to the injection nor were there any changes in the many electrocardiograms taken over a two hour period (figure 4b). The blood pressure varied between 110/86 and 90/70 mm. Hg. Two days later, after administration of a total of 1.0 milligram of digitoxin in dosage of 0.25 mg. every two hours, a normal sinus rhythm was registered (figure 4c).

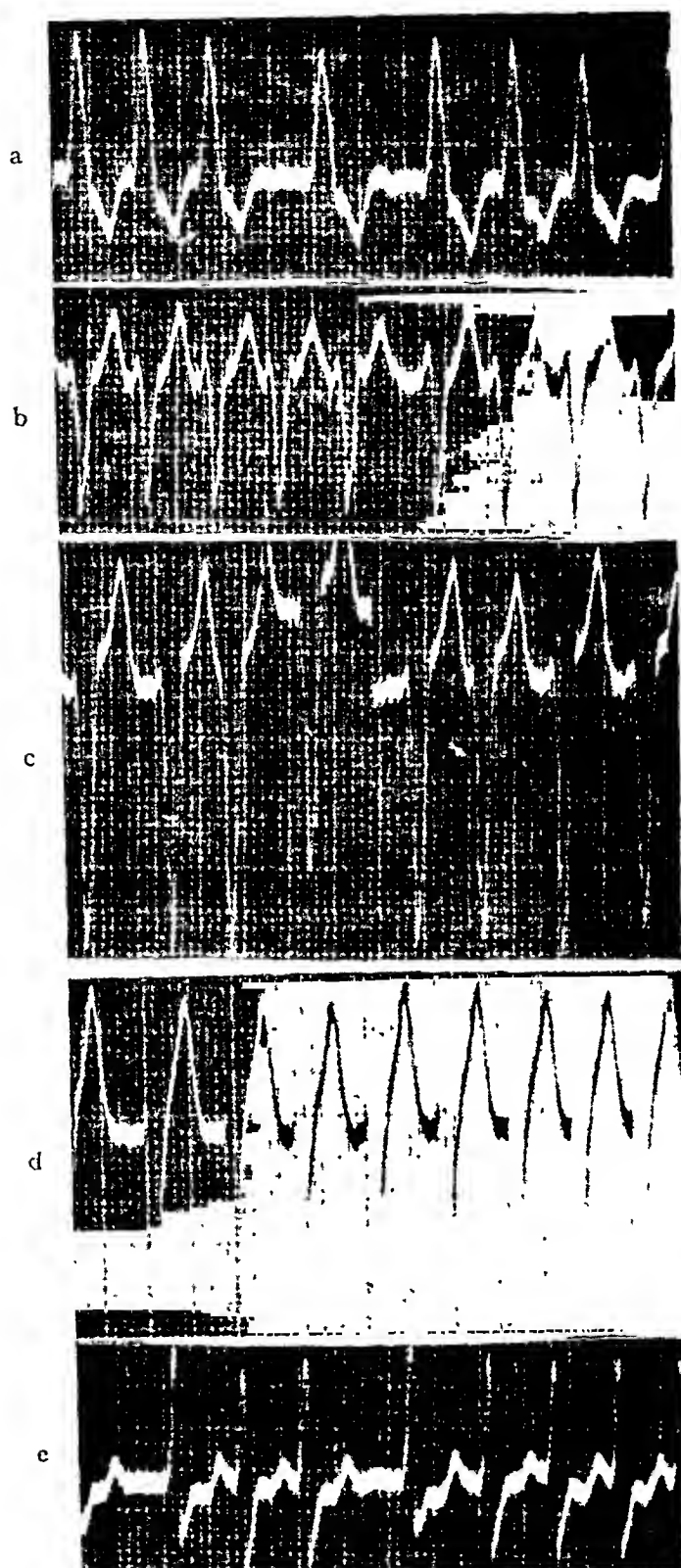


FIG. 2. Three standard leads, leads  $CF_3$ , and  $CF_6$  of case 4 before the injection, showing auricular fibrillation and changes compatible with left ventricular hypertrophy.

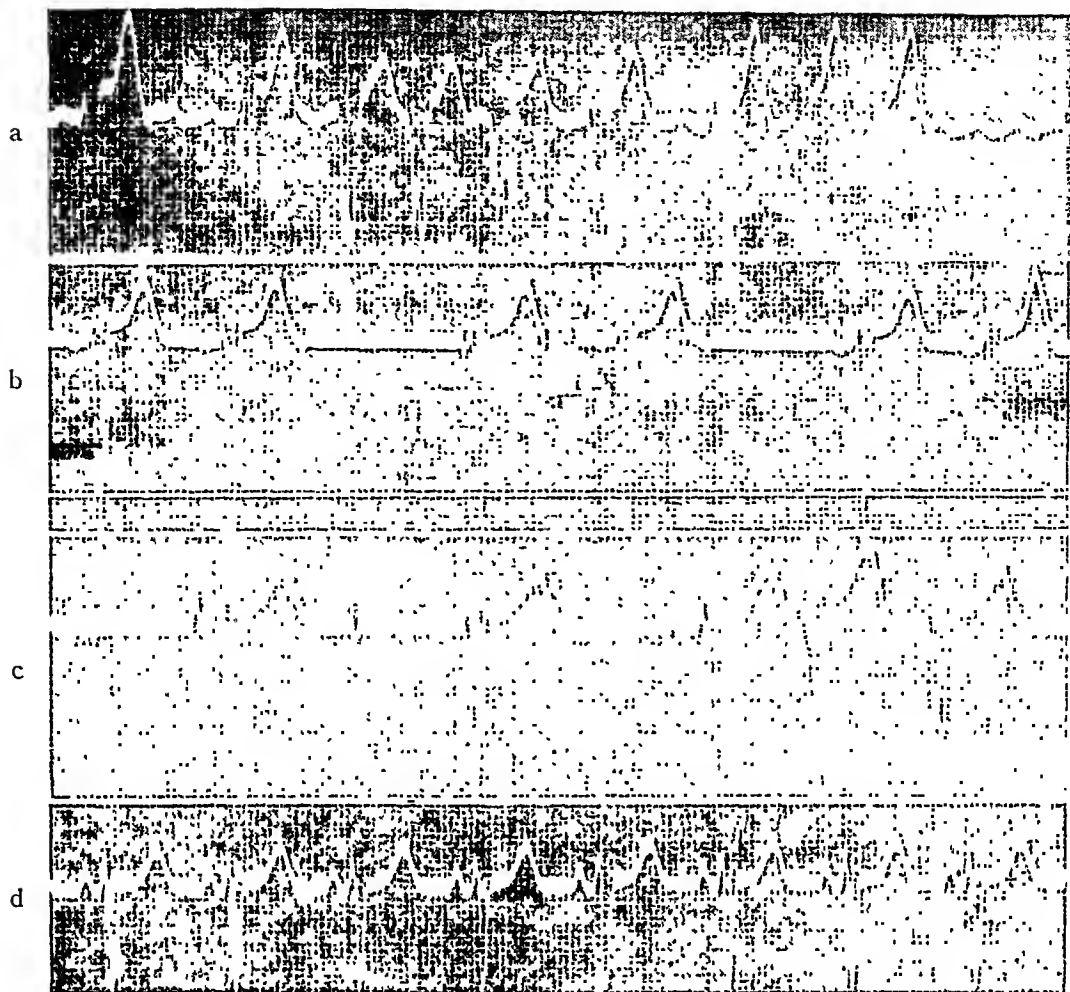


FIG. 3. Figure 3a shows auricular flutter and multiple ventricular extrasystoles 10 minutes after the injection; figure 3b, 3c and 3d were obtained 15, 70 and 180 minutes after the injection respectively (case 4).

*Summary:* 0.1 gram of fagarine was given to a 45 year old woman with paroxysmal supraventricular tachycardia. There was no effect in the electrocardiographic picture of the tachycardia and there were no untoward symptoms from the injection.

*Case 6.* L. C., a 64 year old Chinese male, was admitted in a semi-stuporous condition with left hemiplegia associated with ipsilateral sensory impairment. The heart was enlarged to the left and apical and aortic systolic murmurs were present. The blood pressure was 220/130 mm. Hg on admission and fell to 180/110 subsequently. The patient improved with physiotherapy but was unable to walk or care for himself. Auricular fibrillation with low, slurred, though not widened QRS complexes was noted in the electrocardiogram.

Fagarine in the amount of 0.06 gram was injected. During the following observation period of two hours, there was no change in the blood pressure and no symptoms appeared referable to the injection. The drug was repeated one week later in dose of 0.08 gram, again without appreciable change. The same electrocardiogram with the exception of ventricular extrasystoles originating in one focus was

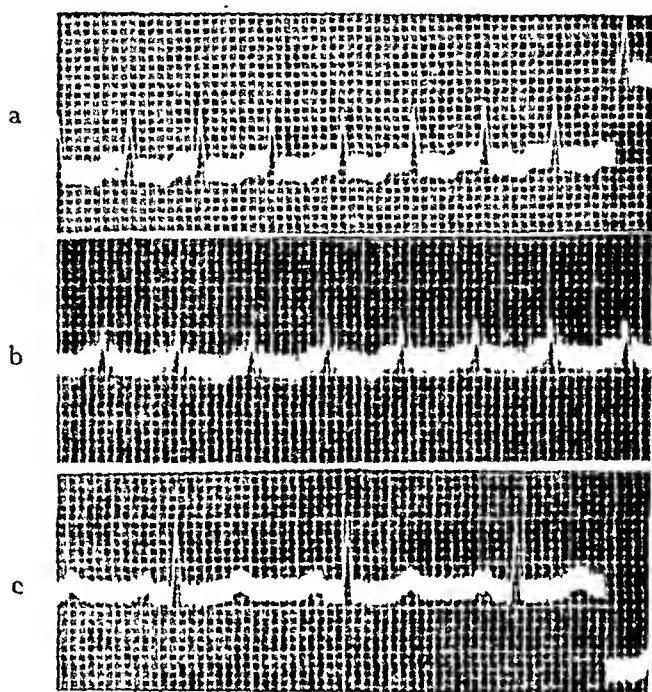


FIG. 4. Figure 4a shows Lead II of a paroxysmal auricular tachycardia recorded before the injection of fagarine; 4b represents Lead II after the injection. Figure 4c shows sinus rhythm two days later, after digitalis administration.

obtained in the two and one-half hour observation period after the injection. The fibrillation persisted.

*Summary:* The injection of 0.06 and again of 0.08 gram of fagarine in a 64 year old man with hypertension and hemiplegia produced no effect.

*Case 7.* A. L., an 88 year old female, was admitted for general weakness and exertional dyspnea. These signs had persisted for a year and had on previous occasions been somewhat relieved by digitalis.

Examination revealed a heart of normal size and shape and a blood pressure of 100/80 mm. Hg. Cheyne-Stokes respiration was present. There was marked dextroscoliosis with emphysema. The liver was slightly enlarged. Blood chemical findings were a nonprotein nitrogen of 135, urea N of 65 and creatinine of 3.2 mg. per cent.

The electrocardiogram showed auricular flutter with a 4:1 block, left axis deviation, and marked slurring of the QRS complexes (figure 5a). After digitalization there was no diminution of the evidence of congestive failure nor of the azotemia. The auricular flutter pattern persisted and therefore fagarine was injected intragluteally in the amount of 0.06 gram.

The blood pressure rose in the following 50 minutes from 108/50 to 136/60 mm. Hg and gradually fell again at the end of 100 minutes to 108/50 mm. Hg; 25 minutes after the injection, the respirations became more forceful and somewhat irregular, but no untoward symptoms appeared.

Ventricular extrasystoles had been present occasionally before the injection (figure 5a), but they increased in number 26 minutes after the injection and were apparently multifocal. Forty-five minutes after the injection, auricular fibrillation appeared (figure 5b) and changed quickly into normal sinus rhythm (figure 5b). Multifocal ventricular extrasystoles appeared (figure 5c).



The patient improved markedly, the evidence of cardiac failure diminished, the blood chemistry became normal, and the patient was finally discharged from the hospital with normal sinus rhythm.

**Summary:** In an 88 year old woman with auricular flutter, the administration of 0.06 gram of fagarine caused transition to auricular fibrillation and sinus rhythm within 45 minutes. Multifocal ventricular extrasystoles appeared as a transient phenomenon in the otherwise uneventful transition.

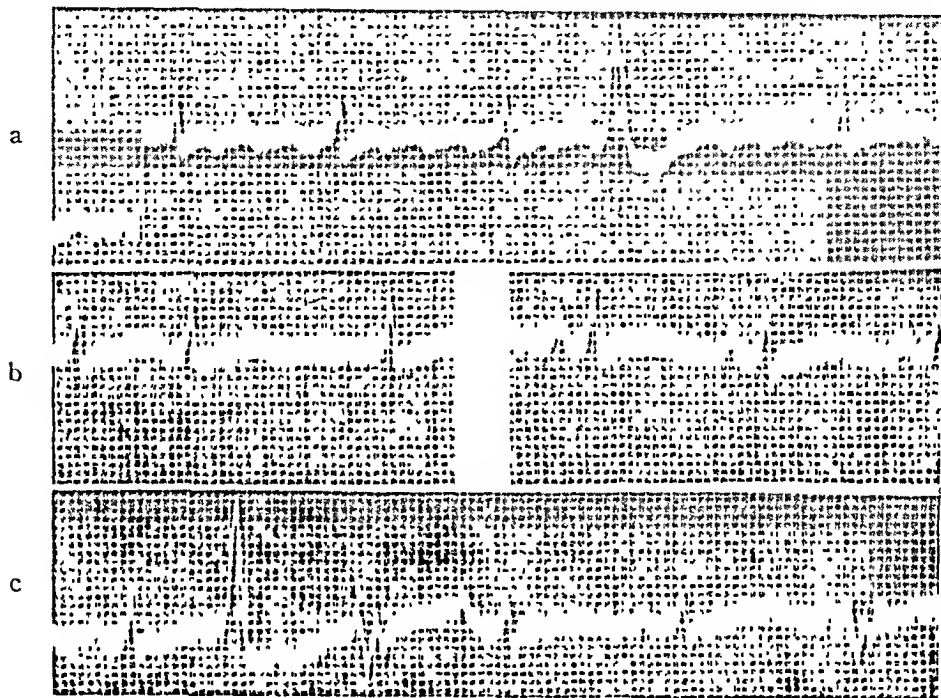


FIG. 5. Auricular flutter and a ventricular extrasystole before the injections are shown in figure 5a (case 7). The first part of figure 5b shows auricular fibrillation, the second part sinus rhythm 45 minutes after the injection. Later multifocal ventricular extrasystoles appeared (figure 5c).

**Case 8.** M. O'B., a 94 year old white male, was admitted to the hospital in a disoriented state. The history was unobtainable until later when the patient said he had suddenly lost consciousness for an indeterminate period prior to admission. Examination showed distant heart sounds and a blood pressure at 130/80 mm. Hg. There was auricular fibrillation. The patient was obviously undernourished and improved rapidly on a high caloric, high vitamin diet without digitalis. Cardiac findings persisted unchanged.

The patient, who weighed 150 pounds, received 0.06 gram of fagarine. Ten minutes after the injection, he complained of slight dizziness and headache; the latter disappeared after 20 minutes, the former after an hour. The blood pressure rose to 140/80 mm. Hg in the first 30 minutes following the injection and fell in the succeeding 60 minutes to 128/68 mm. Hg.

The electrocardiogram prior to the injection showed auricular fibrillation with some slurring of the QRS complexes but no other notable changes (figure 6a). Ten minutes after the injection, multifocal ventricular extrasystoles appeared. These increased in number and in frequency (figure 6b) 20 minutes after the injection. The heart showed regular sinus rhythm 35 minutes after the injection (figure 6c).

Two months later sinus rhythm was still present.

*Summary:* Sinus rhythm appeared within 35 minutes after the injection of 0.06 gram of fagarine to a 94 year old man with auricular fibrillation. Multifocal ventricular extrasystoles, headache, and vertigo followed the injection.

*Case 9.* D. P., a 79 year old male, was admitted in a semistuporous state, confused and disoriented. No history was obtainable. The patient was dyspneic, orthopneic and cyanotic. There were râles over both bases, more marked over the left. The ventricular rate equalled the pulse rate at 160 per minute, but the rhythm occasionally seemed somewhat irregular. The heart sounds were muffled and percussion was unsatisfactory because of emphysema. The blood pressure was 172/80 mm. Hg. The liver was enlarged and there was marked edema of the legs. A hard, irregular sessile mass was palpated rectally and thought to be a carcinoma. The condition of the patient remained very poor; two injections of cedilanide (0.4 mg. each), administered intravenously in 24 hours, were without influence on the tachycardia.

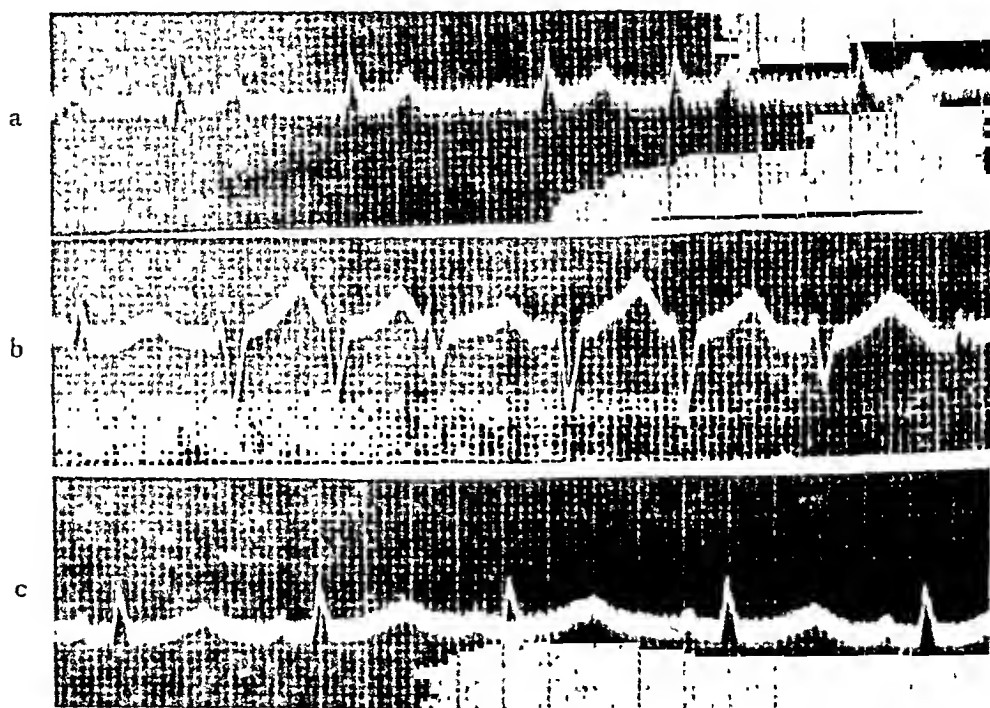


FIG. 6. Figure 6a shows auricular fibrillation before the injection (case 8). Multifocal ventricular extrasystoles are present 20 minutes after the injection (figure 6b), and sinus rhythm appears 15 minutes later (figure 6c).

Fagarine (0.12 gram) was given intramuscularly four days later. The blood pressure fell to 120/70 mm. Hg within 40 minutes, then slowly rose to 158/68. Simultaneously with the fall of blood pressure, a bradycardia appeared.

The electrocardiogram taken before injection of fagarine showed a regular tachycardia with a rate of 133. During the short diastoles, P-waves unrelated to the QRS complexes were occasionally visible (figure 7a). A ventricular tachycardia originating above the bifurcation of the bundle (A-V-nodal or stem tachycardia) with independent activity of the auricle was diagnosed. Six and one-half minutes after the injection the ventricular rate was 93 and the ventricular complexes showed changes which were apparently caused by the slower rate only. Again, the auricles contracted

independently of the ventricles (figure 7b). Twenty-six minutes after the injection the electrocardiogram shown in figure 7c was obtained. Suddenly abnormal ventricular complexes appeared, apparently due to an aberrant ventricular conduction. Some of the ventricular complexes in this tracing were similar to those in figures 7a and 7b, but were wider by 0.02 second and the T-waves were lower. Sixty minutes

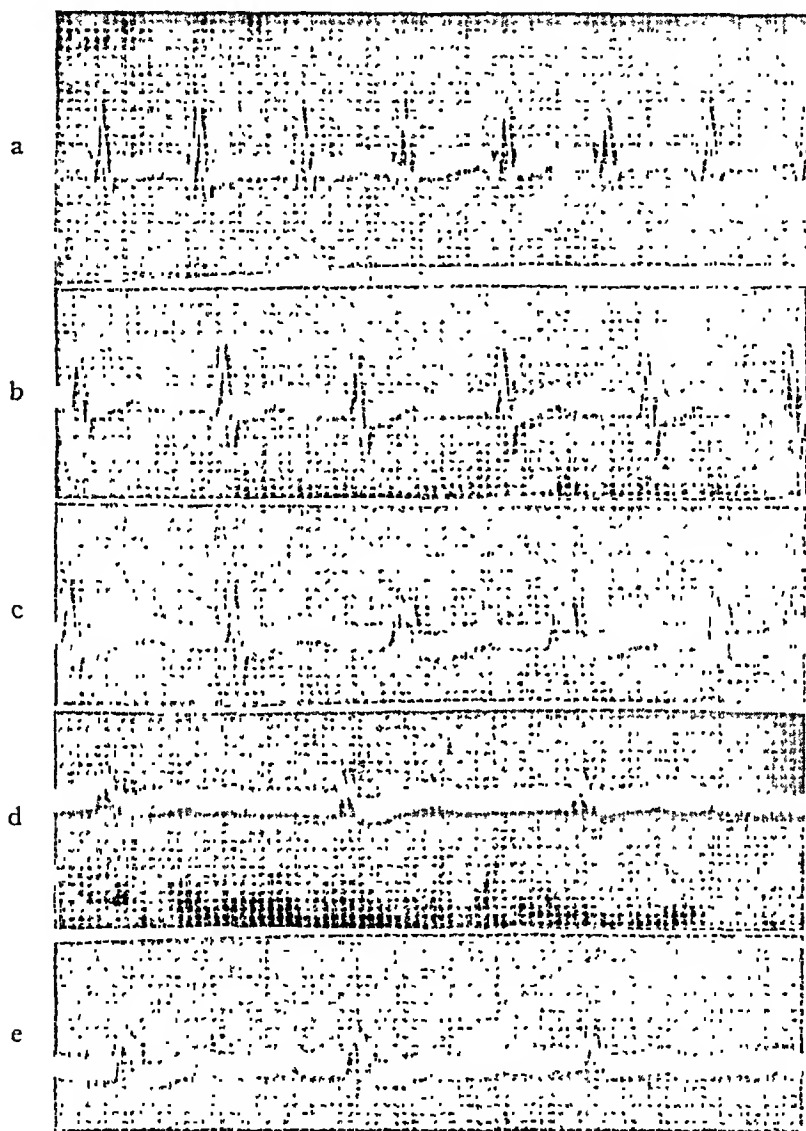


FIG. 7. Figure 7a shows a heterotopic ventricular tachycardia; slowing of the heart and independent action of auricles and ventricles appeared six and one half minutes after the injection (figure 7b). Figure 7c, figure 7d and figure 7e were obtained 26, 60 and 85 minutes after fagarine.

after the injection (figure 7d) the ventricular complexes were lower but otherwise similar to those in figure 7c. The ventricular rate was 58. The auricles contracted irregularly and independently of the ventricles. A similar tracing is visible in figure 7d obtained 85 minutes after the injection. The next morning the electrocardiogram showed the same picture as figure 7a.

The condition of the patient progressively deteriorated and he died on the seventh day of hospitalization.

*Summary:* The injection of 0.12 gram of fagarine in a 79 year old man with systolic hypertension and cardiac failure, presumably the result of coronary sclerosis, and a heterotopic tachycardia, caused only a temporary slowing of the rate and an intraventricular block.

*Case 10.* A. P., a 57 year old woman, was admitted with a history of cardiac disease of many years' duration, but the precise nature of the condition was unknown. The present illness began three days before admission with a cough productive of blood streaked sputum. She experienced palpitation of the heart and had been given 0.2 mg. of digitaline Nativelle daily for two days before admission. A slowly increasing mass in the neck had been noted over a 10 year period; this was associated with increased nervousness, tremor and perspiration. On physical examination, both lobes of the thyroid were enlarged. The heart appeared to be of normal size and the sounds were loud and clear. There was marked hypermotility of the heart. The blood pressure was 140/78 mm. Hg. The heart rate was 128 per minute and auricular fibrillation was present. Râles were present in both bases. The temperature was 39° C. With penicillin the temperature became normal in a few days. She weighed 145 pounds.

An intramuscular injection of 0.1 gram of fagarine was given three days after the last dose of digitalis. Ten minutes after the injection, the pulse became regular. There was no change in the blood pressure and no untoward symptoms followed the injection.

Figure 8 shows the change from the auricular fibrillation to regular sinus rhythm, interrupted occasionally by single or small groups of auricular extrasystoles. Later these disappeared completely. No other changes were demonstrable in the electrocardiogram.

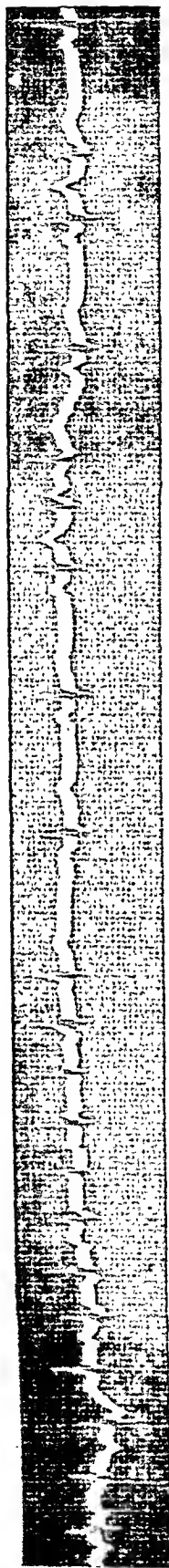
Two days later the auricular fibrillation recurred and persisted continuously. The patient signed her release from the hospital 18 days later.

*Summary:* A 57 year old woman with hyperthyroidism and auricular fibrillation developed sinus rhythm 10 minutes after the injection of 0.1 gram of fagarine. No untoward symptoms were observed.

*Case 11.* M. R., a 70 year old man, was admitted in a semicomatose condition following an accident. Besides a fractured left hip the patient had a very fast pulse with a rate of 136 per minute. Under the mistaken impression that a paroxysmal tachycardia was present, he was given 0.08 gram of fagarine. There was no response clinically and no changes were found in the electrocardiogram; no complications ensued from the injection.

The electrocardiogram taken before fagarine was given (figure 9a) showed a sinus tachycardia with a rate of 136. The

FIG. 8. Change from auricular fibrillation to sinus rhythm 10 minutes after the injection (case 10).



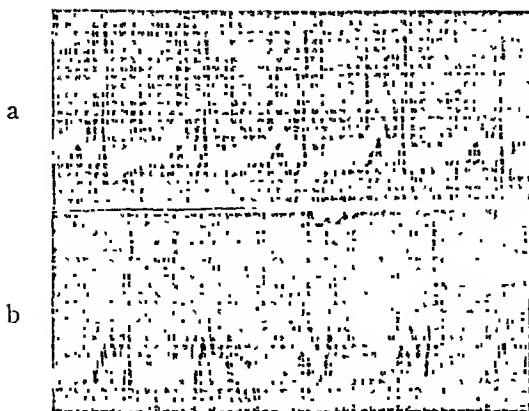


FIG. 9. Sinus tachycardia before (figure 9a) and after (figure 9b) the injection of fagarine (case 11).

same tachycardia with the same rate and the same ventricular complexes was recorded 60 minutes after the injection (figure 9b).

The patient died five days later as a result of his injuries.

*Summary:* A 70 year old patient admitted with sinus tachycardia received 0.08 gram of fagarine without any change in the electrocardiographic picture.

*Case 12.* S. B., an 83 year old male, was admitted with complaints of abdominal distention and absence of bowel movements for one week. On admission the patient was drowsy and displayed muscular twitchings. The pulse was irregular with a rate of 82 per minute, the respiratory rate was 21 per minute. The heart was slightly enlarged to the left and soft mitral and aortic systolic murmurs were heard. The blood pressure on admission was 142/82 mm. Hg. The abdomen was distended and tympanitic. A right indirect irreducible hernia was present. Azotemia was present with a non-protein nitrogen of 120, an urea nitrogen of 71 and creatinine of 3.1 mg. per cent. The electrocardiogram showed auricular flutter with 4:1 block and widened QRS complexes (figure 10a).

Fagarine in the amount of 0.12 gram was injected intramuscularly. The blood pressure was 212/125 mm. Hg. Five minutes after the injection the patient had a seizure of tonic and clonic convulsions with pupils directed upward and with no response to stimuli. He was pulseless and no blood pressure could be obtained. Respirations were about 5 per minute, slow and deep. In two minutes the seizure disappeared and the blood pressure was 210/110 mm. Hg. The pulse was slightly irregular and respirations were normal. The electrocardiogram obtained during the seizure shows that a ventricular tachycardia had appeared with a rate of 230 and with varying forms of the ventricular complexes (figure 10b). Ten minutes after the injection the blood pressure was again 210/120 mm. Hg and the patient appeared the same as before the seizure. Auricular flutter was still present (figure 10c) but the auricular rate had diminished from 330 (figure 10a) to 300. Twenty minutes after the injection there was a second convulsive episode similar to the first which again lasted for two minutes. The electrocardiogram taken during this seizure showed the same picture as figure 10b. A few minutes later the blood pressure rose to 240/120 and the patient again recovered. Thirty minutes after the injection the blood pressure was 180/110 mm. Hg with a full, strong, slightly irregular pulse. The electrocardiogram taken at this time (figure 10d) showed sinus rhythm with occasional

ventricular extrasystoles and a rate of 80 per minute. Forty minutes after the injection the pulse was regular and full but three minutes later another convulsion developed and lasted for five minutes. An electrocardiogram taken during this seizure showed a ventricular tachycardia (ventricular flutter?) with a rate of 230

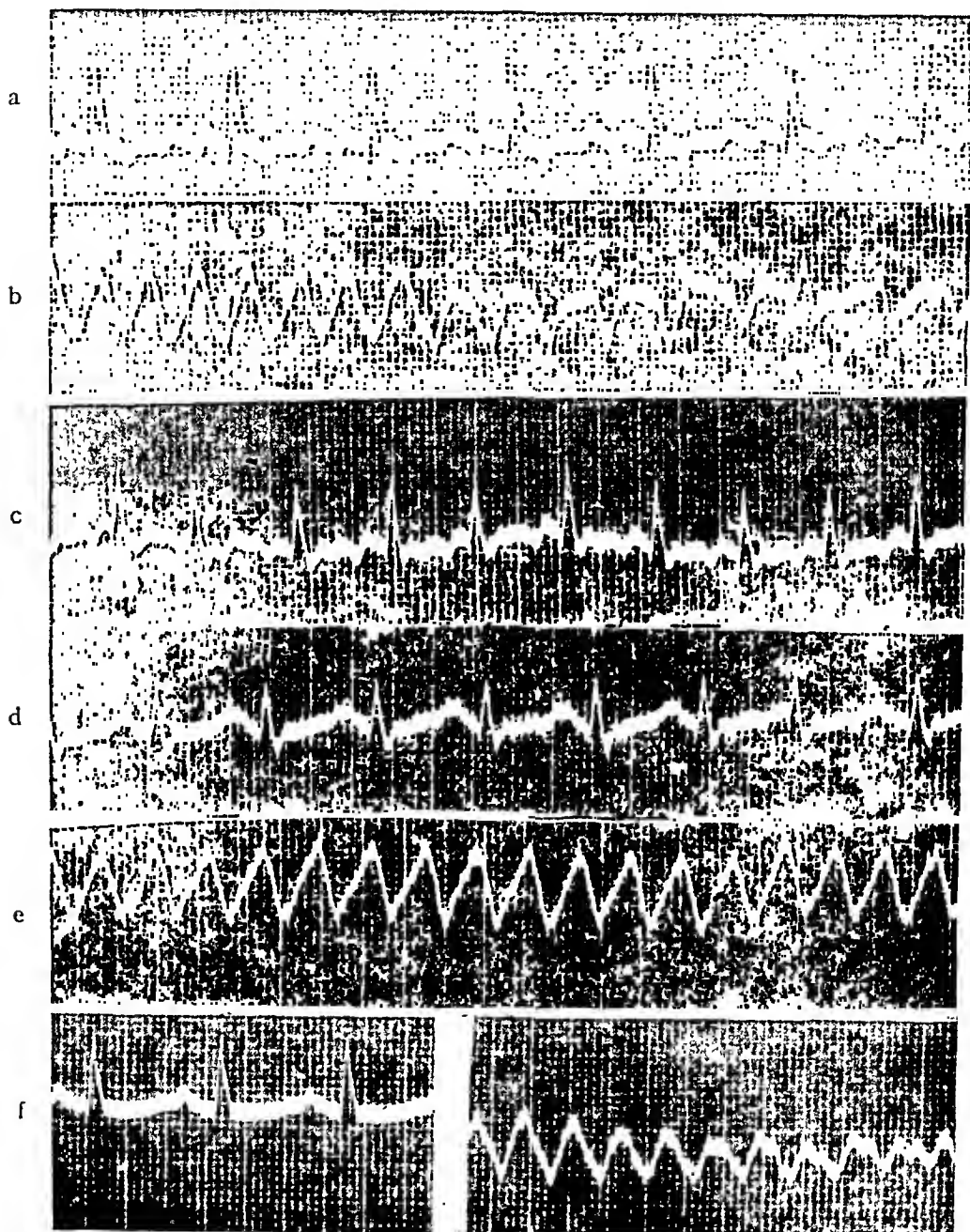


FIG. 10. Figure 10a shows auricular flutter before the injection (case 12). Figure 10b shows ventricular tachycardia during an attack of Stokes-Adams syndrome 5 minutes after the injection. Auricular flutter with slower auricular rate and 2:1 block was registered 10 minutes after the injection (figure 10c), and sinus rhythm was present 20 minutes later (figure 10d). Ventricular flutter appeared 43 minutes after the injection (figure 10e). Sinus rhythm followed by ventricular fibrillation was registered 2 hours after the injection (figure 10f).

(figure 10e). Atropine in the amount of 0.5 mg. was injected intravenously without any noticeable effect. In the following 30 minutes the blood pressure was well maintained and the patient appeared comparatively well. Sinus rhythm was present with a rate of 85 (first part of figure 10f). One hour and 40 minutes after the injection of fagarine the pressure had dropped to 130/70. Exactly two hours after the injection, the patient had his fourth convulsive episode during which he succumbed. The electrocardiogram showed that ventricular fibrillation had appeared with this final episode (figure 10f).

*Summary:* Administration of 0.12 gram of fagarine to an 83 year old man with intestinal obstruction, azotemia, and auricular flutter was followed by sinus rhythm, but an attack of ventricular tachycardia and ventricular fibrillation appeared and led to sudden death.

*Case 13.* S. S., a 72 year old white female whose weight was 150 pounds, was admitted with a history of swelling of the ankles and fullness of the abdomen. These complaints, with breathlessness, had recurred repeatedly for two years.

On admission the patient was dyspneic and disoriented. The heart sounds were loud and pure; there was a rapid heart rate and an irregular rhythm. The blood pressure was 130/90 mm. Hg. The hypermotility of the heart associated with a tremor and exophthalmus suggested hyperthyroidism. Propylthiouracil was administered in the amount of 150 mg. daily and digitalization was started with 0.1 gram of digitalis leaf twice daily.

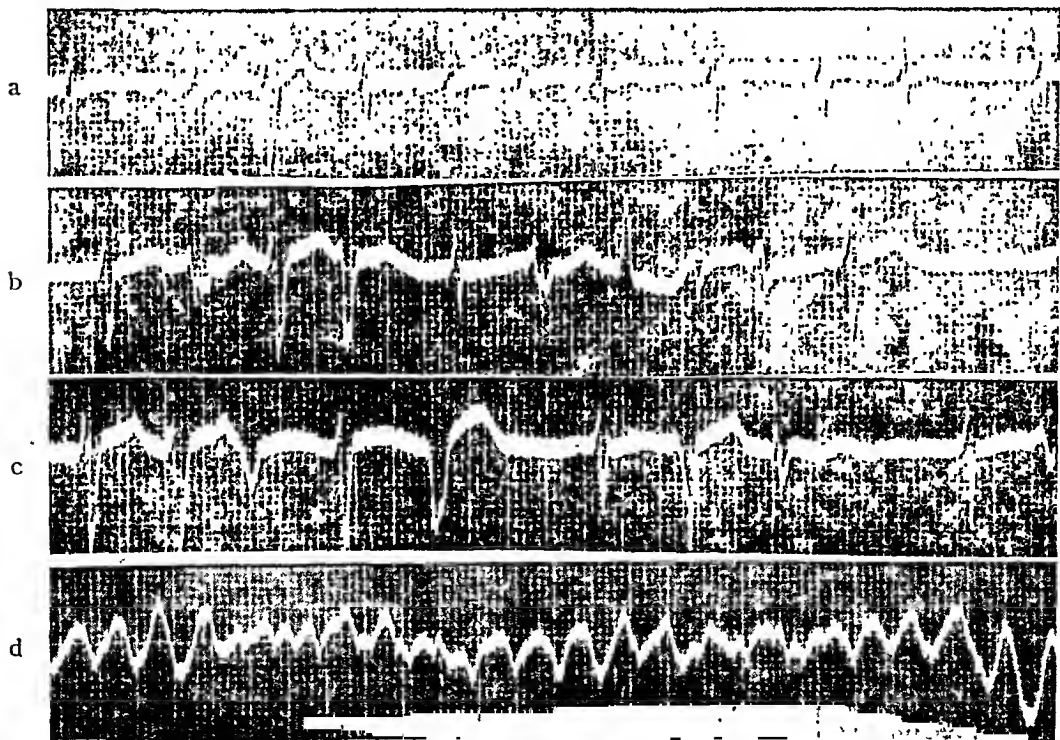


FIG. 11. Figure 11a shows auricular fibrillation and a ventricular extrasystole before the injection (case 13). Multiform ventricular extrasystoles appeared 17 minutes (figure 11b) and 33 minutes after the injection (figure 11c). Ventricular fibrillation appeared 60 minutes after the injection (figure 11d).



The digitalis was discontinued after a trial and 14 days after discontinuation, 0.05 gram of fagarine was injected intramuscularly. There was a drop of 20 mm. Hg of the systolic and the diastolic blood pressures, but otherwise the patient appeared unchanged. However, one hour after the injection the patient suddenly collapsed and soon ceased to breathe.

Figure 11a was obtained before the injection of fagarine and shows auricular fibrillation with a single ventricular extrasystole. Seventeen and 33 minutes after the injection, there was an increasing number of variform ventricular extrasystoles (figures 11b and 11c). The electrocardiographic picture remained unchanged until 60 minutes after the injection when ventricular fibrillation appeared, (figure 11d). At no time was sinus rhythm observed.

*Summary:* In a 72 year old woman with hyperthyroidism and auricular fibrillation, the administration of 0.05 gram of fagarine led to multifocal ventricular extrasystoles and ventricular fibrillation.

### DISCUSSION

The cardiac depressant action of an alkaloid extracted from *Fagara coco* was observed by Stuckert and Sartori in 1932.<sup>9</sup> Fagarine, an alkaloid identical with alpha-fagarina hydrochloride used by us, was later studied experimentally.<sup>4, 5</sup> It was found to raise the threshold of the heart to fibrillation caused by faradization and to diminish the risk of ventricular fibrillation following ligation of coronary arteries. During the wartime scarcity of quinine, Deulofeu and co-workers called attention to fagarine as a remedy for certain tachycardias and fibrillation. In dogs and rabbits it was found that doses of 0.005 gram per kilogram could be given intravenously three times daily for 45 days without incurring immediate or subsequent disturbances.<sup>11</sup> Tacquini gave 0.06 to 0.1 gram of fagarine intramuscularly to six patients with auricular fibrillation. Sinus rhythm appeared in all cases within 40 minutes.<sup>1</sup>

A clinical study of the effect of fagarine on human subjects was conducted.<sup>10</sup> The drug restored sinus rhythm in two cases with auricular flutter and in four of five patients with auricular fibrillation. Sinus rhythm appeared within 20 to 50 minutes after intramuscular administration of the drug. In the six cases where sinus rhythm was restored, the dose employed varied between 0.08 and 0.1 gram. In the patient in whom the drug was unsuccessful, the dose was 0.05 gram. Two of the patients experienced slight dizziness following the injection; one vomited and his electrocardiogram showed multiple ventricular extrasystoles and ventricular flutter. At the Inter-American Cardiologic Congress in Mexico City, Tacquini reported on his further clinical experiences with fagarine.<sup>11</sup> Untoward results were observed in some patients. He warned not to give the drug to digitalized patients. Doses of 0.08 to 0.1 gram were satisfactory. The drug was administered to 25 normal individuals in doses of 0.5, 0.6, 0.7, and 0.8 gram (0.01 gram/kg. body weight). Some patients had previously been completely digitalized, and no toxic symptoms were observed. The Q-T in-



terval was increased in all patients. Depression of the RS-T segment and diminution of the T-wave were seen. The electrocardiographic effects were reduced in most cases when 0.001 gram of atropine was given intravenously. Since doses as small as 0.005 gram per kilogram have a definite effect on cardiac muscle, the author advises starting with a considerably smaller dose which is far below the toxic level.

Data collected from our 13 cases are compiled in table 1. Fourteen injections were given to 13 patients whose ages varied between 45 and 94; eight patients were over 70 years of age. The dose employed was from 0.05 to 0.12 gram. All patients had some disturbance of the cardiac rhythm; in seven patients auricular fibrillation was present, and in three auricular flutter. Five of the patients had hemiplegia, and hyperthyroidism existed in two. The observations on all 13 patients are of interest with regard to their response to the drug. In evaluating the response of an abnormal rhythm to fagarine, two cases must be discarded. In one, the existing auricular flutter had disappeared just before the injection was given, and in the other only sinus tachycardia was present at that time.

In six of the 11 cases, the existing arrhythmia was abolished and sinus rhythm supervened. In one instance the arrhythmia, auricular fibrillation, was not arrested within the two-hour observation period after the injection, but it disappeared within the succeeding 10 hours. Similarly, the auricular fibrillation disappeared four hours after the injection in one case reported by Tacchini.<sup>10</sup> We feel justified in assuming that the fibrillation, which had persisted for many months before the injection, disappeared because of the administration of the drug.

It is difficult to evaluate the effect of fagarine in case 9. A heterotopic tachycardia probably originating in the ventricles above the bifurcation of the A-V conduction system existed. The stimuli formed there were not reversely conducted to the auricles so that the latter contracted independently from the ventricles. Following fagarine the tachycardia disappeared temporarily and a slow heterotopic ventricular rhythm appeared.

We consider this a successful use of fagarine. The return of the tachycardia after the fagarine effect wore off is to be expected in certain types of tachycardias (*extrasystolies à paroxysms tachycardiques*).<sup>3, 7</sup>

Our tenth case, similarly, demonstrated a return of auricular fibrillation within two days. This finding would be anticipated in many cases of hyperthyroidism.

Most regrettable were the accidents in the last two cases, where the injection was certainly the cause of the appearance of ventricular fibrillation.

In case 12 the first attack of Stokes-Adams syndrome caused by pre-fibrillary ventricular tachycardia or ventricular flutter, appeared only five minutes after the injection. In view of the rapidity of onset and of the existing azotemia, it seemed probable that the condition of the patient made his response to the injection abnormal. We decided, therefore, to continue the investigation. The next injection was given to a patient in good gen-

TABLE I

Case No.	Initials	Age	Sex	Clinical Diagnosis	Prevailing Rhythm	Fagarine Dose in Grams	Effect of Fagarine	Side Effects in ECG	Other Side Effects
1	P. M.	86	F	Hemiplegia, generalized arterio-sclerosis	Auricular fibrillation	0.06	No immediate effect; sinus rhythm next morning	0	0
2	A. M.	87	M	Generalized arterio-sclerosis	Sinus rhythm	0.06	0	0	0
3	R. M.	65	F	Diabetes mellitus, pneumonia, hemiplegia	Auricular fibrillation	0.09	No effect	0	Buzzing in the ears
4	C. G.	68	M	Hypertensive cardiovascular disease, hemiplegia	Auricular fibrillation	0.12	Sinus rhythm	Many ventricular extrasystoles, sinus arrhythmia, A-V block	0
5	M. Y.	45	F	Paroxysmal tachycardia	Paroxysmal supra-ventricular tachycardia	0.10	No effect	0	0
6	L. C.	64	M	Hypertensive cardiovascular disease	Auricular fibrillation	0.06 0.08	No effect No effect	Ventricular extrasystoles	0
7	A. L.	88	F	Emphysema, generalized arterio-sclerosis, azotemia	Auricular flutter	0.06	Sinus rhythm	Multifocal ventricular extrasystoles	0
8	M. O'B.	94	M	Generalized arterio-sclerosis	Auricular fibrillation	0.06	Sinus rhythm	Ventricular extrasystoles	0
9	D. P.	79	M	Hypertensive cardiovascular disease	Heterotopic tachycardia	0.12	Bradycardia, intra-ventricular block	Multifocal ventricular extrasystoles	0
10	A. P.	57	F	Hyperthyroidism	Auricular fibrillation	0.10	Sinus rhythm	0	Headache, vertigo
11	M. R.	70	M	Hip fracture	Sinus tachycardia	0.08	No effect	0	0
12	S. B.	83	M	Hypertensive cardiovascular disease, hemiplegia, intestinal obstruction	Auricular flutter	0.12	Sinus rhythm followed by ventricular fibrillation	Ventricular flutter and fibrillation	Stokes-Adams attacks due to ventricular flutter and fibrillation
13	S. S.	72	F	Hyperthyroidism	Auricular fibrillation	0.05	Ventricular fibrillation	Multifocal ventricular extrasystoles	0

\* Received two injections in successive weeks.

eral condition and the amount was only 0.05 gram. Unfortunately, the patient developed lethal ventricular fibrillation even before the auricular fibrillation disappeared. The hyperthyroidism itself, though it may have increased sensitivity to fagarine, was most probably not the only factor involved in the accident, because another patient with hyperthyroidism and of approximately the same body weight (case 10) tolerated 0.1 gram of fagarine very well. With this unfortunate and dramatic experience the investigation was immediately stopped. We are unable to decide whether the simultaneous administration of propylthiouracil was responsible for the regrettable accident.

Multifocal extrasystoles appearing in patients with coronary sclerosis, myocardial infarction, or following administration of digitalis or strophanthin are always an ominous sign. They occurred in five patients in addition to the one (case 13) who developed ventricular fibrillation. It is notable that in one observation (case 12), ventricular flutter and fibrillation supervened without the appearance of multifocal extrasystoles. Such extrasystoles are often seen following ligation of the coronary arteries in the experimental animal, but occasionally ventricular fibrillation starts without the preceding appearance of extrasystoles.

In case 6 the administration of 0.06 gram of fagarine caused no response while the injection of 0.08 gram, a few days later, was followed by the appearance of ventricular extrasystoles. Multifocal ventricular extrasystoles were also seen by Tacquini in one observation.<sup>10</sup>

In case 12, not only was there extremely rapid disappearance of auricular fibrillation, but an early onset of ventricular fibrillation with death. In view of the appearance of ventricular fibrillation in two cases and a serious augmentation of ventricular extrasystoles in others, the risk engendered in the use of fagarine is great. It is to be stressed that four cases showed no response to the drug and in these cases, despite the administration of relatively large doses (up to 0.1 gram), there were no changes in the existing rhythm.

Except in the last two cases the untoward symptoms were trifling. Only headache, buzzing in the ears, and vertigo occasionally appeared. There were no complaints in eight patients. The electrocardiographic changes were also slight. We confirmed the observations of Tacquini who also saw prolongation of the Q-T interval, depression of the S-T segment and lowering of the T-waves. Because of the smaller doses employed in our studies, these changes were of lesser extent and frequency than in the observation of Tacquini.

Remarkable is the early appearance of the effects of the injection in some cases. In case 4 distinct changes were visible within 10 minutes and in case 10 the auricular fibrillation changed into sinus rhythm after the same time interval. Case 8 showed multifocal ventricular extrasystoles 10 minutes after the injection. In case 12 the first attack of ventricular flutter appeared only five minutes after the injection. Great care was always taken to avoid an intravenous injection.

It is of interest that in case 4 fagarine changed auricular fibrillation into auricular flutter before sinus rhythm was established, while in case 7 flutter gave way to fibrillation before sinus rhythm appeared.

Only in one patient were respiratory alterations in form of more forceful breathing observed (case 7). The abnormal respiration in case 12 was certainly the consequence of the disturbance of the activity of the ventricles.

The point has already been stressed that death occurred in one of our cases who received 0.12 gram, which was the largest dose employed by us, and in another patient of approximately the same weight after a dose of 0.05 gram. The dose of 0.12 gram had previously been administered to two other patients in both of whom multifocal ventricular extrasystoles appeared. The slightly smaller dose of 0.1 gram was tolerated well without complications. On the other hand, in one patient the dose of 0.05 gram was followed within 25 minutes by ventricular fibrillation. While most other patients were in very poor physical condition, case 13 was not very ill. Case 7 had ventricular extrasystoles before the administration of fagarine and developed multifocal extrasystoles afterward.

Following the intravenous injection of fagarine in dogs a temporary moderate rise of blood pressure was observed.<sup>6</sup> We found a similar rise in four cases (cases 3, 4, 7, 8). Occasionally a temporary fall was seen (case 1) or a moderate rise *and* fall, as in case 9.

It is, in general, rarely necessary to abolish auricular fibrillation; most of the cases are treated successfully with digitalis and rarely does their condition further improve if they are "defibrillated." If defibrillation seems necessary, one succeeds in most cases with oral administration of quinidine. The same holds for the paroxysmal tachycardias. Only rarely is one unsuccessful in abolishing a tachycardia through one of the vagal reflexes or with oral administration of quinidine. Too frequently the physician immediately tries one of the injectable preparations recommended for this purpose. Such injections must be given if the vagal reflexes are ineffective or if quinidine is not tolerated or does not produce results. We recently lost a 46 year old patient with a fresh myocardial infarction, who developed a paroxysmal ventricular tachycardia which did not respond to quinidine, even in the dose of 6.0 grams daily. For such cases an effective and non-toxic drug is highly desirable. In cases of auricular flutter occasionally digitalis and quinidine, even in large amounts do not bring about a change to fibrillation or sinus rhythm; therefore treatment with other drugs becomes desirable and necessary. Unfortunately, our experiences do not show fagarine to be the ideal drug for these indications. The search for such a substance should be continued and justifies, in our opinion, the investigation reported in this paper. Recently investigations<sup>2</sup> show that it might be possible to detain non-toxic and effective antifibrillatory agents, related to fagarine.

Previous digitalization is considered a contraindication to the use of fagarine by Tacchini and his colleagues.

The observation of depression of abnormal, heterotopic stimulus formation and simultaneous excitement of stimulus formation in other centers is observed with many other well known substances often used in cardiology. Thus digitalis may both suppress and excite abnormal stimulus formation in the form of extrasystoles and tachycardias. Potassium salts may also abolish or cause ventricular fibrillation and it seems clear that the mode of action does not depend on the dose alone. Even quinidine and quinine, which are the best known substances for abolishing arrhythmias, may cause extrasystoles<sup>12</sup> and, even in relatively small doses, cause ventricular fibrillation if given intravenously.<sup>8</sup> We therefore think that in spite of the unfortunate experiences in cases 12 and 13 the drug should not be discarded peremptorily and experimental studies with it should be continued. We feel particularly encouraged by its action in animal experiments where doses up to 0.004 gram/kg. given *intravenously* to dogs by one of us<sup>6</sup> were tolerated well and always immediately abolished auricular flutter or fibrillation; no extrasystoles or other disturbances of rhythm appeared. Furthermore, huge doses were given to patients with healthy hearts by Tacchini without untoward results.<sup>11</sup>

### SUMMARY

Fourteen intramuscular injections of alpha-fagarine hydrochloride were given to 13 patients, whose ages varied between 45 and 94. Eight patients were over 70 years old. The dose varied between 0.05 and 0.12 gram. In six patients the existing arrhythmia disappeared promptly after the injection. In two patients, however, fatal ventricular fibrillation appeared. In five other cases dangerous multifocal ventricular extrasystoles were observed.

The response of the 13 patients to the drug is discussed in detail. Fagarine cannot, as yet, be recommended for clinical use. Further experimental studies with this interesting drug may lead to the discovery of an active and non-toxic agent.

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# XANTHOMATOUS BILIARY CIRRHOSIS (A CLINICAL SYNDROME) \*

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EVIDENCE of skin xanthoma with chronic jaundice and liver disease in relatively rare cases has been recognized for a long time and recorded in the literature by various authors: Addison and Gull,<sup>1</sup> 1851; Moxon,<sup>2</sup> 1873; Pye-Smith,<sup>3</sup> 1873; Hutchinson, Sangster and Crocker,<sup>4</sup> 1882; Balzer,<sup>5</sup> 1884; Hardaway,<sup>6</sup> 1890; Fitcher,<sup>7</sup> 1905; Posner,<sup>8</sup> 1909; Chvostek,<sup>9</sup> 1911; Dyke,<sup>10</sup> 1928; Weidman and Freeman,<sup>11</sup> 1924; Buerger,<sup>12</sup> 1934; Weidman and Boston,<sup>13</sup> 1937. However, no attempts were made to match various characteristic symptoms to a definite clinical entity. Thannhauser and Magendantz<sup>14</sup> in 1937 and Thannhauser<sup>15</sup> in 1940 described as "xanthomatous biliary cirrhosis" a typical clinical syndrome characterized by the following features:

1. Skin xanthoma of the "plain and tuberous" variety.
2. Enlarged liver and spleen.
3. Obstructive type of jaundice of years' duration.
4. Extremely high values for total cholesterol (increased four to eight times those of normal) as well as for lecithin (increased four to eight times those of normal in serum).
5. The serum is transparent and not creamy despite the outstanding increase of cholesterol and lecithin. Low values for neutral fat in the serum are found.

Since the publication of Thannhauser and Magendantz's paper similar observations have appeared by Comfort, Shepard, and Snell,<sup>16</sup> Herbert,<sup>17</sup> Eusterman and Montgomery,<sup>18</sup> and Layani, Laudat and Astruc,<sup>19</sup> Hoffbauer, Evans and Watson,<sup>20, 21</sup> and Gebhardt.<sup>22</sup> Thannhauser and Magendantz in 1937 were not in a position to report autopsy findings of their cases.

Moxon and Fagge<sup>23</sup> as well as Pye-Smith (1873) reported autopsies of three cases showing xanthoma of the skin and atheromatous changes on the inner lining of the arteries as well as xanthoma formation on the lining of the bile ducts. Pye-Smith described the changes in the liver as revealing a slight degree of interstitial cirrhosis. "The patches in the ducts looked just like atheroma in the artery with which condition, indeed, they corresponded histologically."

Depending on these findings, Thannhauser and Magendantz suggested

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that xanthoma formation of the larger bile ducts producing xanthomatous scar tissue may be the cause of the clinical syndrome described as xanthomatous biliary cirrhosis. It was their opinion that the development of the xanthoma of the skin as well as the xanthoma formation on the lining of the bile ducts was the expression of a systemic disease characterized by increased new formation of cholesterol and hypercholesteremia (hypercholesteremic xanthomatosis). The xanthomatous involvement of the large bile ducts and their partial obstruction was thought to be the primary event which resulted later in this special type of biliary cirrhosis.

In the meantime autopsies were performed on three cases of xanthomatous biliary cirrhosis, none of them showing xanthomatous changes of the lining of the bile ducts. It is the purpose of this paper to clarify the mechanism which may lead to the development of the well-defined clinical syndrome of xanthomatous biliary cirrhosis. The detailed clinical histories and laboratory findings of five cases observed over a long period, three autopsies, and four biopsies at our disposal taken at an early stage of the disease will provide the basis for this report.\*

#### CLINICAL CASES WITH AUTOPSIES AND BIOPSIES

*Case 1.* D. L. M., a 44 year old French-Canadian woman, was admitted to the Joseph H. Pratt Diagnostic Hospital in November 1939. The patient stated that she had been perfectly well until 1937 when she first noticed icterus of her sclerae and skin. Although at that time she had no abdominal pain, she became severely nauseated and vomited every morning. She developed anorexia and lost about 30 pounds within four months. She also observed severe pruritus of the skin, especially of her arms. She had no fever or chills. Her stools were clay-colored. Her urine was a deep orange.

In May 1938 she had been hospitalized at the Boston City Hospital for 10 days. She was placed on a liquid syrup diet. The patient stated that the jaundice of her sclerae and skin decreased considerably. After her discharge she faithfully kept to her diet. However, three months later jaundice of the skin and sclerae is again increased. There was only slight pruritus. The patient did not have fever, chills or abdominal pain. Her stools again became clay-colored. Her urine was persistently deep orange. Although the jaundice varied in intensity, it was always present to some extent.

In January 1939 the patient noticed a yellowish discoloration and elevations along the creases of both palms. These lesions were progressive. In June 1939 she observed a small flat yellowish plaque along the inner canthae of both eyes. These plaques progressed rapidly involving the upper and lower eyelids. As far as the patient knew, there were no other yellowish spots, nodules or papulo-pustular eruptions on her body.

The patient complained of tiredness, weakness and listlessness. After a fall, three to four weeks before her admittance to the hospital, she had constant pain in the lower lumbar region and a sharp pain between the shoulder blades radiating around

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the left chest wall to the left inframammary region. This pain, which developed in the evening, was not related to exertion, exposure to cold air or to eating of heavy meals. It was not relieved by rest. The patient had no headaches or sinus trouble. Her vision had been blurred. She has had no diplopia. She has had no ear or nose symptoms. Her teeth were in poor condition. For the previous two to three years she had a cough producing yellowish-whitish sputum. She had no hemoptysis or pleuritic pains, no exertional dyspnea, orthopnea, ankle edema or angina pectoris. There had been no recent nausea or vomiting. Her appetite had been improving. She took mineral oil every morning prophylactically. However, she was not constipated and had no diarrhea. Her stools were clay-colored, usually normally formed and not frothy or foul in odor. She had nocturia once or twice a night but no dysuria, hematuria or pyuria. Her urine was persistently deep orange. The patient complained of recent nervous feelings. She had noticed a tingling sensation in both hands and wrists for over a year.

Her habits were regular. She ate three times a day. She had meat in the form of liver and steaks as part of her antianemic diet, and fruit juices for liver trouble. She has had insomnia. Formerly she had worked as a night club hostess for three years and drank more than her share of liquor. She had taken practically no alcohol in the previous 18 months.

The patient's father had died of heart trouble at the age of 50; the mother of carcinoma of the uterus at 52. The mother's father had died of carcinoma of the stomach. The mother's sister had diabetes. There was no history of xanthomatosis in the family.

Physical examination showed a small, deeply jaundiced woman with temperature of 97° F. The skin over the arms was brownish colored. There was also a combination of lemon-yellowish and brownish jaundice on the palms. A small nodule was located in the right occipital region of the scalp. Rather extensive xanthelasmas were present in the inner canthi and along both the upper and lower lids. Those in the upper lid were more marked, measuring 3.5 to 4 cm. in length and about .5 cm. in width. They were also elevated 1 to 2 mm. above the level of the skin. The conjunctivae were not pale. Several small irregular nodules were found in the right inferior palpebral conjunctiva. The sclerae were deeply jaundiced. The fundi were not remarkable, and there was no lipemia retinalis. The mucosa of the hard palate was jaundiced. No yellowish nodules were seen on the buccal or pharyngeal mucosa. There was a small yellowish elevated nodule about 3 mm. in diameter over the ankle of the right foot. A small wide yellowish plaque of 12 mm. and another of pinpoint area were observed in the right antecubital space. No nodules were found on the extensor surfaces of the elbows and knees. There were slightly elevated yellowish deposits, a few mm. in width, along most of the flexor creases of both palms. These were most marked at the metacarpophalangeal creases of the thumb. In some interspaces they extended almost to the dorsum of the hand. The reflexes were normal.

The lungs were normal. The apex impulse of the heart was felt 9 cm. to the left of the midsternal line in the fifth interspace. The area of cardiac dullness was not enlarged by percussion. The rate was 76 per minute, and the rhythm was regular. No murmurs were heard. The vessels were not arteriosclerotic. The radials were equal and synchronous. Blood pressure 135 mm. Hg systolic and 85 mm. diastolic.

The abdomen was soft without tenderness or rigidity. The liver, markedly enlarged, especially on the right side of the abdomen, extended up into the left hypochondrium. The spleen was not definitely palpable but was enlarged by percussion. No other masses were felt.

Roentgen-ray examination: The liver was extremely enlarged. The spleen and kidneys appeared to be within normal limits. There was no roentgenological evidence of esophageal varices.

Laboratory data: Urine, amber color, cloudy, reaction acid, gravity 1.007, slightest possible trace of albumin, negative sugar, normal urobilinogen, rare red and white cells. Blood sedimentation rate was 86 mm. at the end of one hour by the Westergren method. Hemoglobin 69 per cent or 9.5 grams; red blood cells 3,210,000; white blood cells 11,450; color index 1.08; differential count showed 74 per cent polymorphonuclears, 1 per cent bands, 2 per cent eosinophiles, 1 per cent basophiles, 19 per cent lymphocytes and 3 per cent monocytes. The smear showed some anisocytosis, macrocytosis and microcytosis. The platelets appeared normal.

The patient was discharged from the hospital with a diet almost free of animal cholesterol and low in animal fats. Vegetable fats like olive oil and peanut oil were allowed.

January 12, 1940: This patient reported that she kept her diet. The jaundice seemed unchanged. *Liver*: Four fingers below the costal margin, firm and smooth surface. *Spleen* definitely enlarged and palpable two fingers below the left costal margin. Constant itching of skin. (Chemical analysis of serum, see table 1.)

June 1, 1940: The skin xanthoma did not change although the patient adhered rigidly to her diet. Liver enlargement not diminished. Spleen became larger, two fingers below the left costal margin. The patient complained about pain in her stomach two to four hours after she ate, which awakened her in the early morning hours. As she was already on a vegetarian diet, low in fat but high in carbohydrates, no special diet change was made. (Blood chemistry, see table 1.)

February 7, 1941: Gastrointestinal complaints unchanged. Liver and spleen enlargement unchanged. Jaundice as well as skin xanthomas not increased. (Blood chemistry, see table 1.)

July 22, 1941: Roentgenologic studies showed a double ulcer of the duodenum. Stool examination for occult blood slightly positive. Patient had had profuse vaginal bleeding the previous week. Gynecological examination: vaginal polyp and fibromatous uterus. (Blood chemistry, see table 1.) Cholesterol-free diet continued.

November 14, 1941: (Blood chemistry, see table 1.) Because of increasingly constant stomach pain, an exploratory laparotomy was performed by Dr. F. H. Clute (November 20, 1941) and revealed a double duodenal ulcer. It was not resected. At this time a *liver biopsy* was taken (figures 1 to 6). Postoperative course was uneventful. No bleeding.

January 7, 1942: Abdominal discomfort from the ulcer continued. The patient believed she had contracted an upper respiratory infection a few weeks before. She coughed and produced a fair amount of whitish mucous sputum.

July 25, 1942: Cough and sputum were less. Her main complaint now was the itching of the skin. Liver and spleen still enlarged. Jaundice and skin xanthomas unchanged. (Blood chemistry, see table 1.)

December 10, 1942: Patient had lost considerable weight (10 to 15 lbs.) in the past two weeks. She developed a high temperature running up to 103°, which continued from that time. Roentgenograms of the lung unfortunately were not taken.

January 16, 1943: The patient was hospitalized again because of her extreme weakness and high temperature. *Lungs*: over both lungs fine moist consonating râles were heard. No dullness. *Liver and spleen* were greatly enlarged. No ascites. No evidence of ankle edema. Xanthomas and jaundice unchanged. Spider veins were noted on several places of her skin. (Blood chemistry, see table 1.) The patient was believed to have pneumonitis. The sputum was not examined for tubercle bacilli. Roentgenograms of the lung were not taken. The patient became progressively weaker and died on February 27, 1943. Until her death, she was conscious and not in a hepatic coma (blood chemistry, see table 1).

*Pathologic Report*: The biopsy specimen received in December 1941 was wedge shaped and measured 1.5 by 1 by 0.8 cm. It included capsule and underlying liver

TABLE I  
Lipid Analysis of Case D. L. M.

	Cholesterol free diet							Fever due to tuberculosis			Normal
	11-27-39	1-12-40	6-1-40	2-7-41	7-22-41	11-14-41	1-7-42	7-25-42	1-16-43	2-27-43	
Total cholesterol	1460.0 mg. %	1140	840	1040	670.0	870	830	444	258	death	150-260 mg. %
Free cholesterol	155.0 mg. %	406	250	300	310.0	135	134	99	137		40-70 mg. %
Cholesterol present as esters	1305.0 mg. %	734	590	740	360.0	735.0	696	345	121		70-75% of total cholesterol
Total phospholipids	2300.0 mg. %		1572					1000	1880		150-250 mg. %
Cephalin	30.0 mg. %										10-30 mg. %
Lecithin	2120.0 mg. %										140-220 mg. %
Total fatty acids	1970.0 mg. %										200-450 mg. %
Neutral fat fatty acids	0										0-250 mg. %
Neutral fat	0										0-250 mg. %
Bile acids	5 mg. %	8	6.44		3.4 mg.						0-2
Bilirubin	dir. 6.60 indir. 6.60		indir. 5.4 dir. 3.6	8.6 tot. 6.0 alb. 3.6 glob.	5.3 dir. 7.3 indir.					total 19.50	
Serum protein					6.5 tot. 4.1 alb. 2.4 glob.						
Phosphatase (Bodansky U)						1 hr. 115	1 hr. 125	1 hr. 54		10	1-4 $\mu$
Blood sediment rate	1 hr. 86				98 1 hr.						

tissue. There was no gross thickening or irregularity of the surface. Many sections were made and each was entirely free of subcapsular fibrosis, a condition commonly seen in blocks of liver taken from the gall-bladder area. In each section between 50 and 100 portal areas could be readily counted. This afforded a fair and adequate interpretation of the underlying disease. Preparations of this size removed without trauma or coagulation are very much better than fragments extracted by needle biopsy.

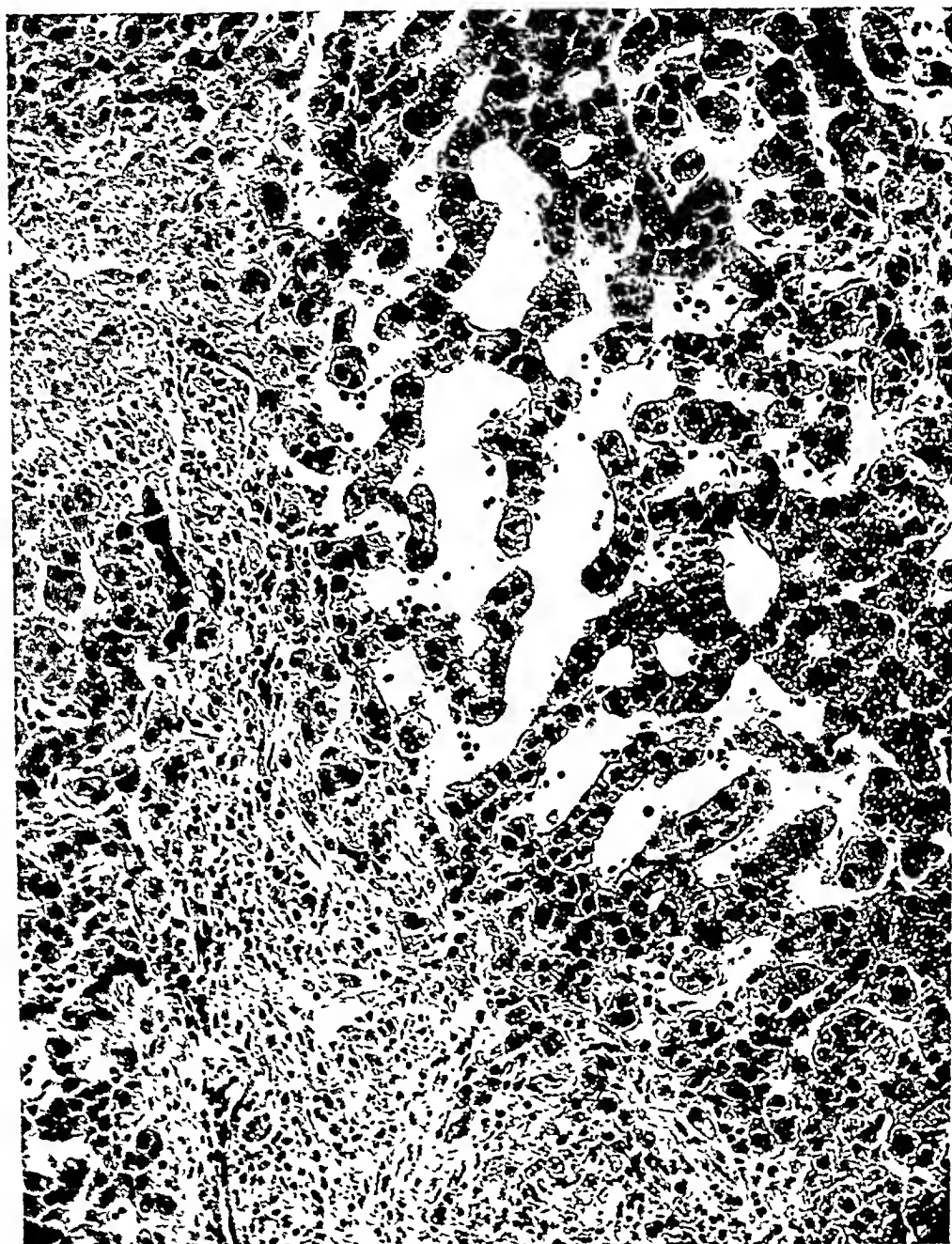


FIG. 1. Liver. This field was selected to show a portion of the peripheral zones of two lobules together with an inflamed and thickened portal area. It shows an extension of the inflammatory process into the lobule with compression of some sinuses and dilatation of others.

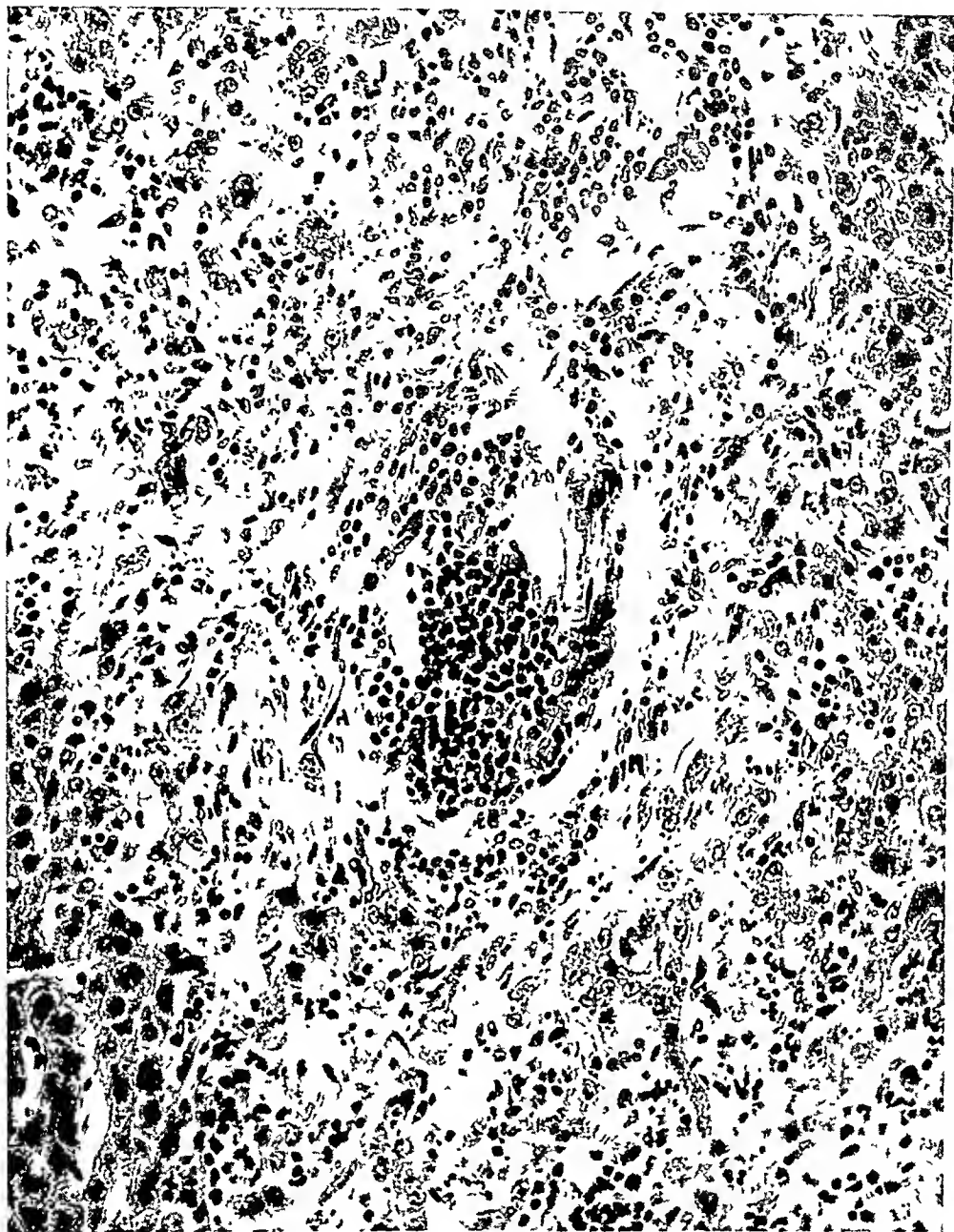


FIG. 2. Liver. This field was selected to show an inflamed and widened portal area. There is a rich cellular infiltration. There is an increase in inflammatory granulation tissue and there is an extension of this inflammatory reaction into the peripheral zones of the lobule. No bile ducts are visible in this field, but liver cells are so compressed that they resemble terminal cholangioles. The only suggestion of a portal vein is the presence of several compressed and slit-like endothelial lined spaces.

*Microscopic Findings:* The pattern of the liver was well preserved and all portal areas, lobules and central veins were easily identified. The pathological change was centered in the perilobular or portal connective tissue. This change involved all portal areas, but the lesions varied in size. No portal area in any of the sections could be considered normal. The lesion was characterized by a non-specific, subacute to chronic inflammatory reaction centered at the junction between portal area and

lobule (figure 1). It was characterized by a proliferation of fibroblasts, the formation of new capillaries, a light deposition of collagen and a variable infiltration of cells. These included neutrophils, lymphocytes, monocytes, plasma cells, eosinophils and very, very rarely, a multinucleated giant cell.

The small bile ducts so readily seen in the portal areas of healthy livers could not be identified. The lymphatics and terminal branches of the portal vein were com-

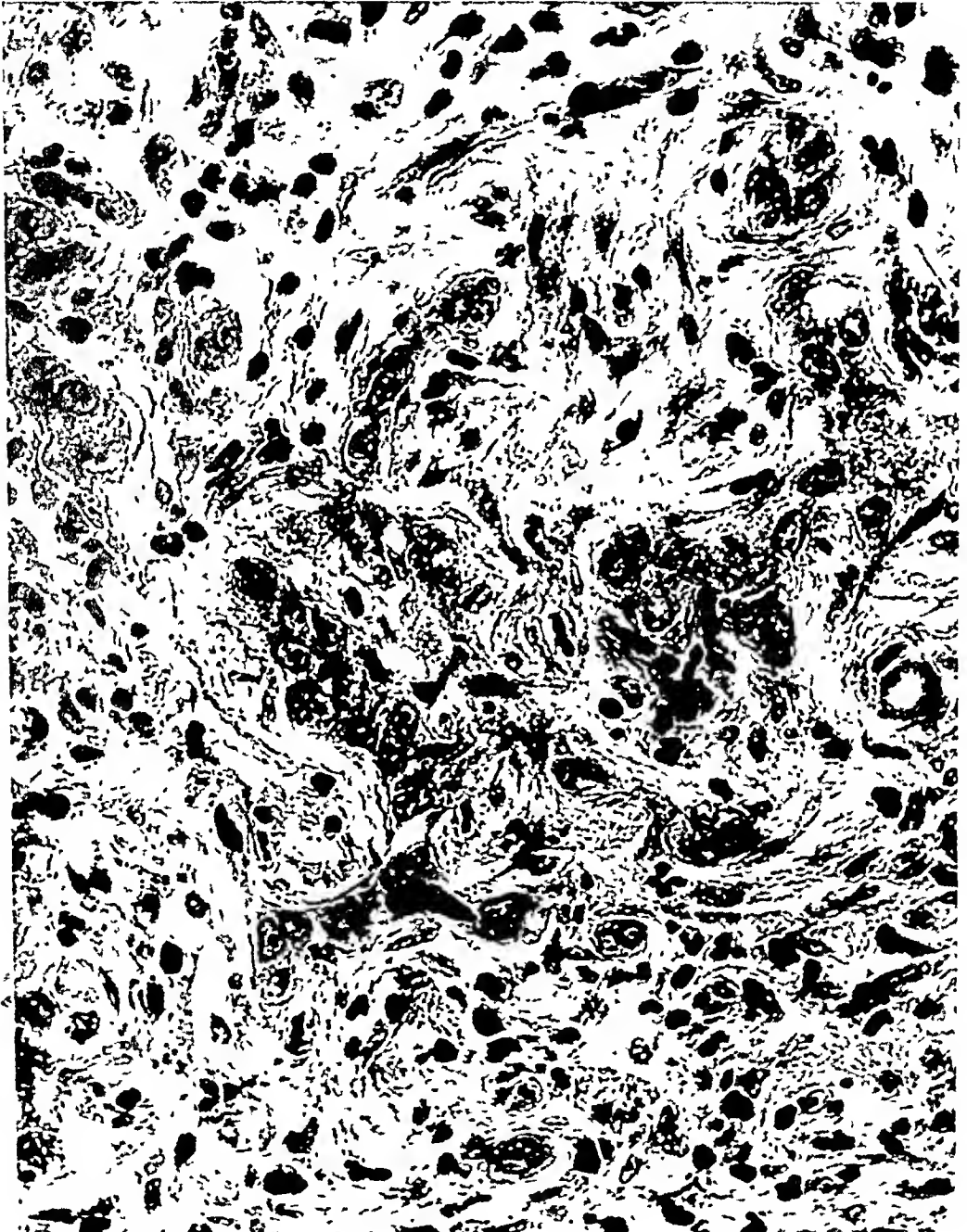


FIG. 3. Liver. This is a higher power magnification of a field at the periphery of a lobule. It shows the increase in fibrous tissue extending into the lobule surrounding and compressing cords of liver cells. Neither the sinuses nor the sinus endothelium is recognizable. The sinuses are now filled with inflammatory granulation tissue.



pressed, narrowed and in areas obliterated by inflammatory granulation tissue (figure 2). The small arteries were unchanged.

This inflammatory reaction originating in and radiating out from the portal areas led to a variable and often irregular expansion of the perilobular connective tissue. The picture suggested a spilling over of inflammatory tissue from the portal areas into the peripheral zones of the lobules. The lines of demarcation between portal connective tissue and lobules were poorly defined because of this infiltration of inflammatory granulation tissue into the bordering parenchyma.

In the beginning the reaction is centered about the terminal bile ducts and is confined to the portal areas. From here it spreads into the most peripheral portion of the lobule by infiltrating along the perisinusoidal spaces of Dissé. In this manner liver cells, singly and in cords, become bordered by inflammatory granulation tissue (figure 3). The sinus at first narrowed by this increase in fibroblasts later disappears. At this stage the histological picture suggests a solid wedge of granulation tissue separating and compressing intact and broken cords of liver cells. In the early stages the marginal liver cells remain unchanged, but later when they become engulfed in fibrous tissue they show a series of regressive changes. Some of them swell to twice their normal size and accumulate vacuoles in their cytoplasm. In some the cytoplasm becomes granular and eosinophilic. Other liver cells accumulate bile and still others show necrosis and disintegration.

Signs of liver cell regeneration were found in the peripheral zones of lobules (figure 4). This was shown by the presence of mitotic figures. The very few small bile ducts that were visible in the portal areas were so compressed and flattened that they resembled solid cords of endothelial cells. There were no leukocytes or bile casts within the lumina of any of these bile ducts. The junction ducts or canals of Hering, so difficult to see in a normal liver, were accentuated by the ingrowth of inflammatory granulation tissue.

Bile stasis was a striking finding. First, there were large and small casts of inspissated bile in the canaliculi of collapsed and compressed cords of liver cells. Secondly, there were coarse clumps of bile in liver cells bordering the portal areas. There was no bile retention within the central zones of the lobules. This seemed paradoxical, for this is the common site of bile retention in simple extra-hepatic biliary obstruction.

The sinuses adjacent to the portal areas were sometimes dilated and sometimes compressed. The lining endothelial cells were, for the most part, inconspicuous, but here and there an isolated endothelial cell was laden with lipoid. The central veins and sublobular veins, with few exceptions, showed no sign of inflammatory granulation tissue (figure 5).

Rarely the inflammatory reaction in the portal area cut deeply into the lobule and in one field a continuous track of granulation tissue could be traced from the portal area to the central vein (figure 6). The type and extent of the cellular exudate warrant a more detailed description. In some fields the cellular infiltration was minimal. In other areas, it so dominated the field that it obscured completely the underlying granulation tissue. One field showed nests of polymorphonuclear leukocytes, another was dominated by lymphocytes and histiocytes.

To summarize the overall picture, it may be said that the liver was the seat of an active, subacute to chronic inflammatory reaction centered in the portal areas. This was characterized by an increase in inflammatory granulation tissue with a corresponding widening and lengthening of the portal connective tissue. There was a tendency for portal areas to unite and to form thin barriers of perilobular fibrosis. There was bile stasis within the lobules and many of the sinuses were narrowed or blocked. The nature of the reaction may be distinguished from the changes seen in obstructive and cholangitic biliary cirrhosis though its distribution is similar to that

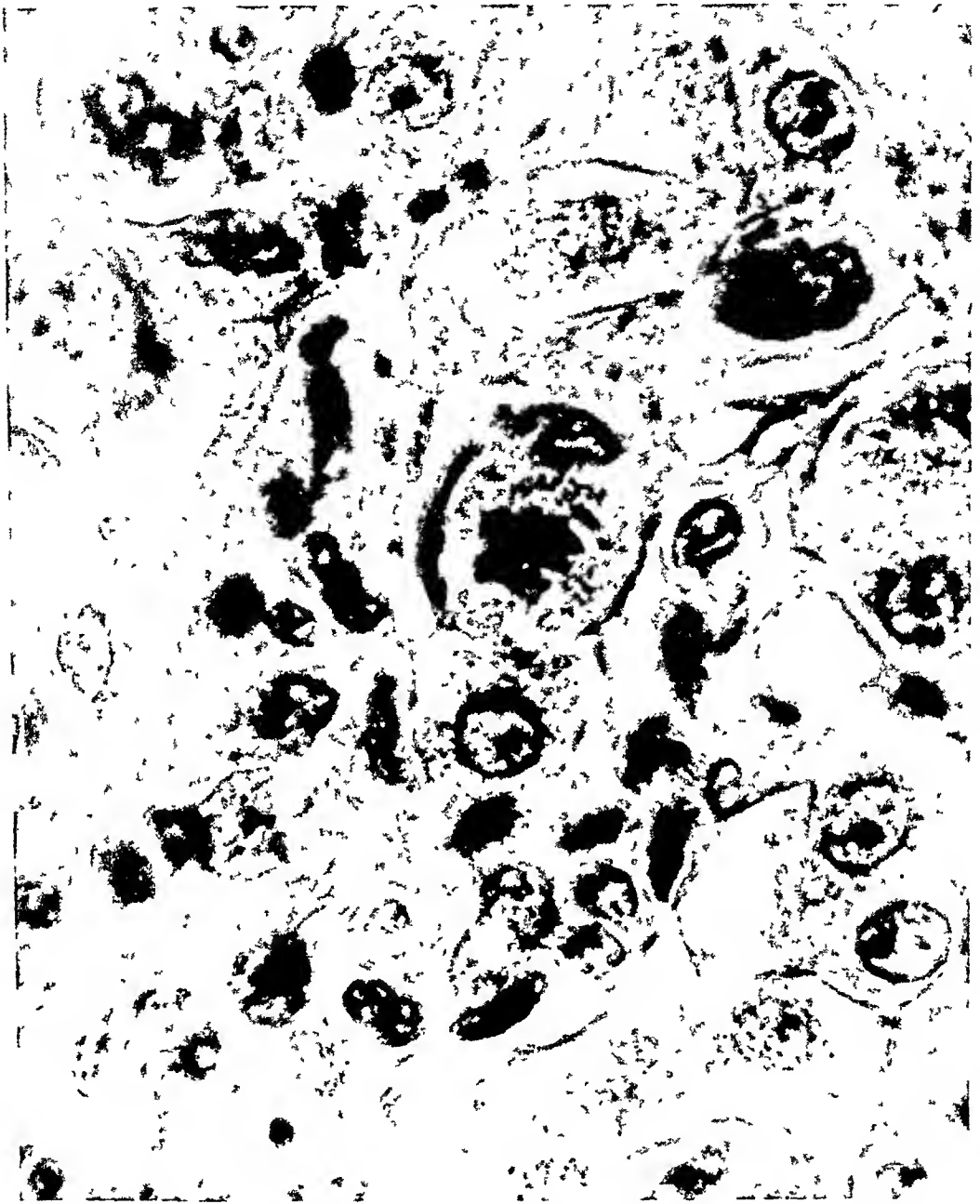


FIG 4. Liver. This field was selected to show a liver cell in mitosis. The cell is swollen and larger than those bordering it. The nuclear membrane is lost and the chromatin forms a coarse cluster in the center of the cell.

of both of these forms of cirrhosis. Because the lesion is centered about the terminal bile ducts and because it is characterized by an inflammatory process, and particularly because at the present time the etiology remains obscure, the name pericholangiolitic biliary cirrhosis is suggested.

*Autopsy Findings:* The liver was large, uniformly granular and bile-stained. On section, the freshly cut surface showed a lobular, but coarse, pattern. There was absolutely no suggestion of any type of extra-hepatic biliary obstruction and no lipid was seen in any part of the biliary tract.



*Microscopic Findings:* The histology of the liver was now much more complex than in the biopsy taken 14 months previously, for now the pathology was much older and it was complicated by a very recent and terminal miliary form of tuberculosis.

The pattern of the liver was badly distorted. The portal areas were wide, branching, irregular and rich in fibrous tissue. They reached out into the lobules

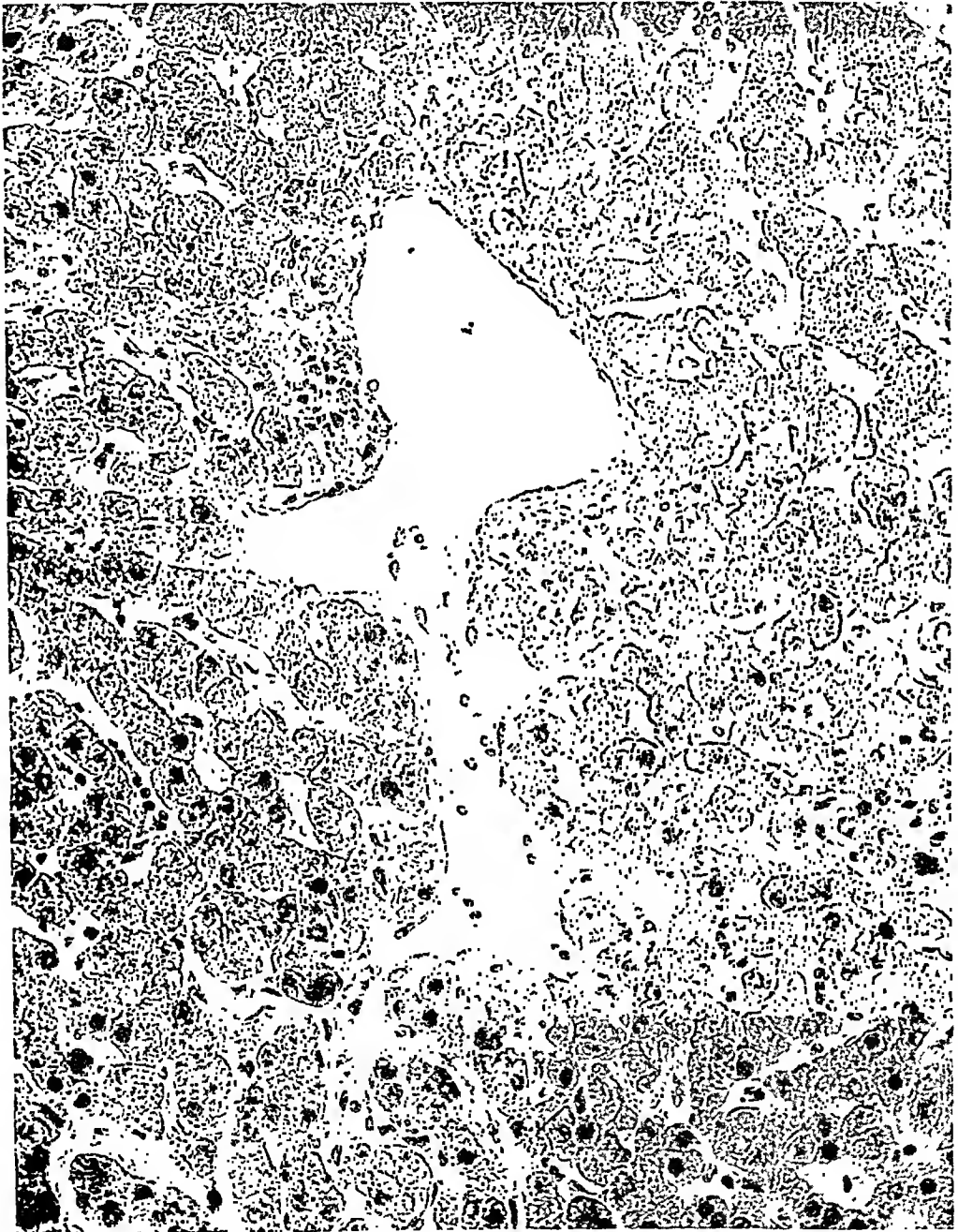


FIG. 5. Liver. This field was selected to show the junction of a central vein with a sublobular vein. The vessels are dilated and contain few cells. The endothelial cells lining the vessel are flat and inconspicuous. The surrounding liver cells are orderly and bear a normal relationship to sinus endothelium. There is no trace of inflammation. Fields of this sort were common and stood out in sharp contrast to the changes going on in the periphery of the lobule.

and broke them into smaller and irregular nodules. There were nodules of regenerated liver cells. The liver parenchyma was edematous and delicate fibrous strands extended far along the sinuses into the lobules (figure 7). Some of the sinuses were collapsed, some were distended with blood; some contained nests of endothelial cells laden with lipoid. Many of the liver cells showed hyaline degeneration. Lastly, there were tubercles in every field.

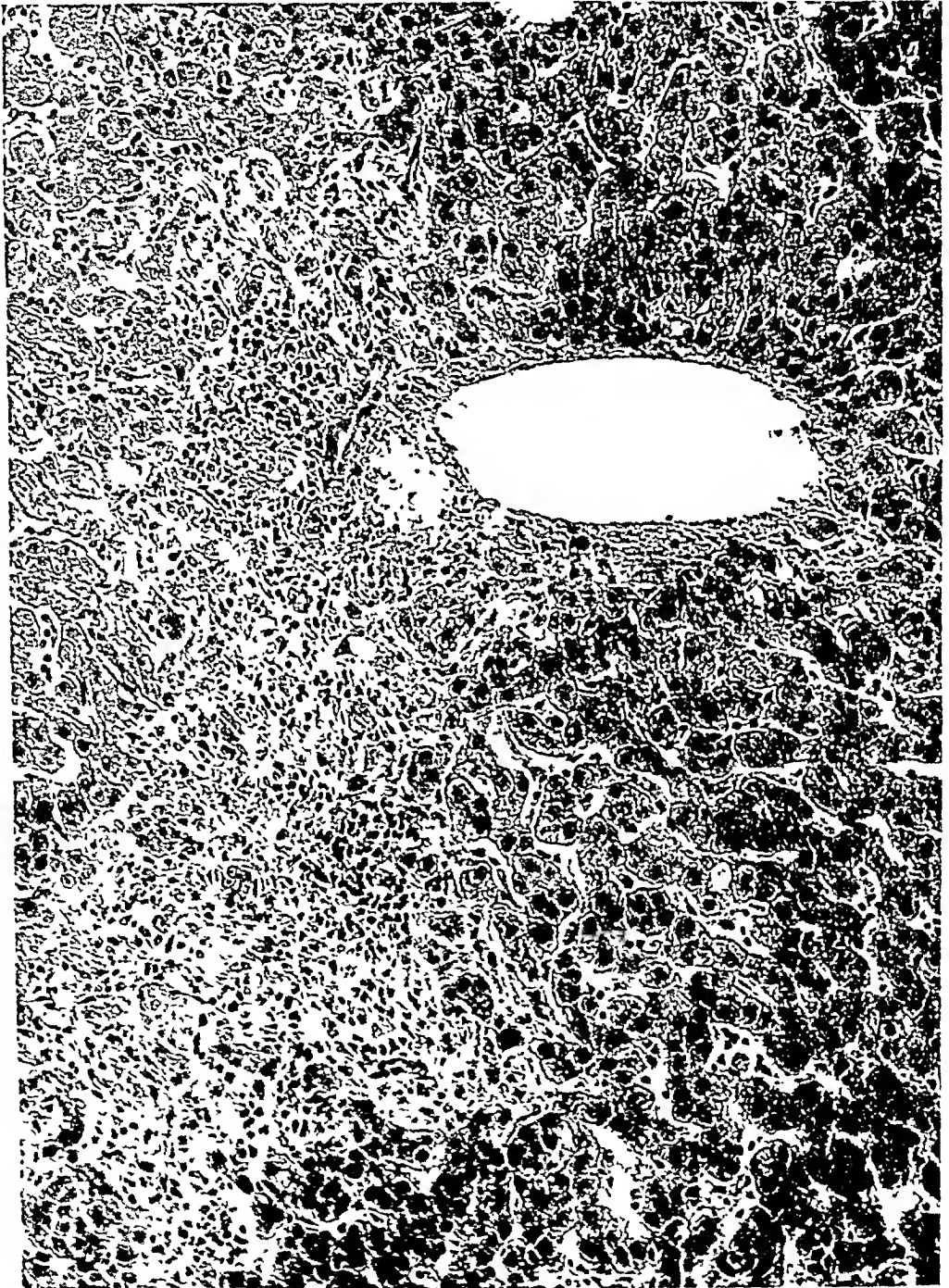


FIG. 6. Liver. This field was selected to show the extension of an inflammatory process from the adjacent portal area out to the edge of a central vein. The central vein itself is dilated and most of the surrounding lobule is free of pathology.

The large size of the liver, the diffuse and extensive fibrosis, the intracellular bile stasis and the still active inflammatory reaction in the portal areas offered a very complex histological picture. It is interesting to compare the liver now with the biopsy studied months earlier. Common to both is the bile stasis, the hyaline degeneration of liver cells (figure 8), and the widening of the portal areas. In the biopsy, the lobular pattern was retained, at the time of autopsy there was little of the original pattern recognizable. The large bile ducts at the hilus of the liver and

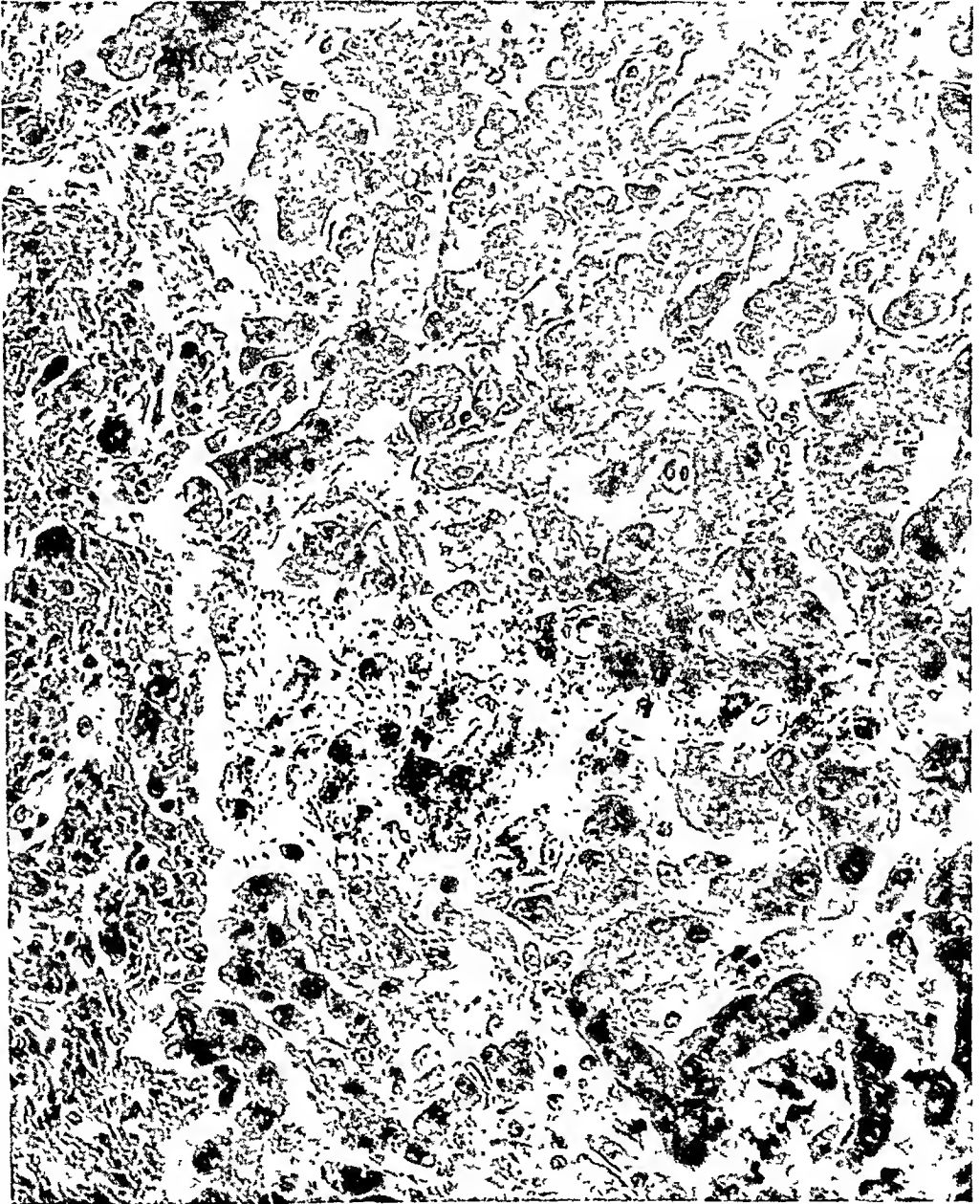


FIG. 7. Liver, at the time of autopsy. This field was selected to show a portion of the peripheral zone of a lobule or nodule of liver cells bordering an area of fibrosis. The cords of liver cells are tortuous and widely separated. The sinuses contain large lipoid-laden histiocytes. There is a moderate increase in perisinusoidal collagen. The sinuses are collapsed and poorly defined.

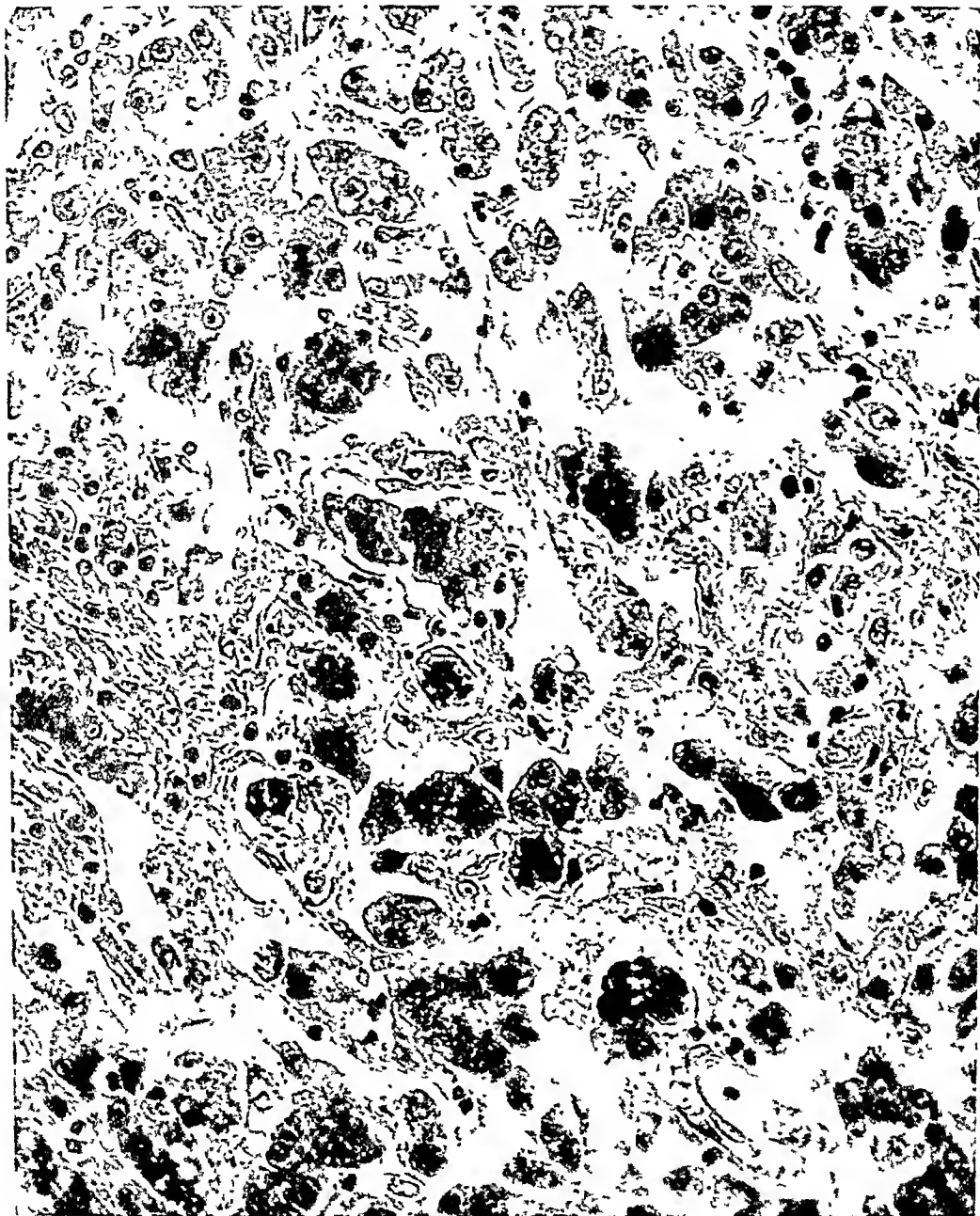


FIG. 8. Liver. This section is from the liver at the time of the autopsy. This field was selected to show a group of liver cells, adjacent to a portal area, containing large deposits of coarse, eosin-staining hyaline. The cords of liver cells are broken up and the sinuses are collapsed by perisinusoidal edema and fibrosis.

radiating throughout the liver were collapsed and empty. In none of the intrahepatic bile ducts were xanthoma cells demonstrable. The classification of this type of cirrhosis, when seen for the first time in its end stages at the autopsy table, is puzzling and often uncertain. It is difficult to realize that a lesion that begins in the portal areas can lead to such destruction.

*Clinical Comment on Case D. L. M.:* The patient exhibited during the first two years of observation the typical characteristics of xanthomatous

biliary cirrhosis suggested by Thannhauser and Magendantz: (1) Skin xanthomas (xanthelasma of eyelids, tuberous xanthomas on elbows, xanthomas of the creases of the palms). (2) Enlarged liver and spleen. (3) Obstructive type of jaundice with bilirubin giving the direct and indirect van den Bergh reaction. (4) Extremely high values in the total cholesterol (1460 mg. per cent, about 85 per cent present as esters) as well as for lecithin (2120 mg. per cent, about 10 times normal). (5) The serum is transparent despite the high cholesterol and lecithin content. Neutral fat is not present in measurable amounts.

Thannhauser<sup>24</sup> suggested that the accumulation of cholesterol and lecithin in the serum at the outset of xanthomatous biliary cirrhosis may be caused by an increased formation of these substances in the liver by a functional disturbance of the liver cells. Histological examination of this patient's liver had already revealed in the early stages fibrotic changes in and around the finest bile capillaries. At this point it seems appropriate to consider which of three possibilities is concerned with the pathogenesis of the disease: (1) whether the assumption of an increased formation of cholesterol and lecithin in the liver is justified, (2) whether these substances are retained in the serum only by an impaired elimination due to fibrotic obliteration of the finest bile capillaries; or (3) whether both processes, namely increased formation and retention cause the high values for cholesterol and lecithin in the serum. The clinical and laboratory findings during almost three years of observation of this unique case provide the basis for such a discussion. An increased formation of cholesterol and lecithin may be indicated by the following findings.

1. The total cholesterol of the serum, 1460 mg. per cent on an unrestricted diet, could not be reduced lower than about 800 mg. per cent cholesterol and 1000 mg. per cent lecithin on a diet free of animal cholesterol and fats. These high cholesterol and lecithin values were maintained during the period of diet treatment for two and a half years (see table 2). This observation suggests that an excessive endogenous production of cholesterol and lecithin persisted while the exogenous quota of animal cholesterol supplied by food was meanwhile almost completely restricted.

2. The cholesterol concentration in the serum decreased markedly and was almost normal in the final period of the disease possibly because an intercurrent tuberculous disease with miliary dissemination in the liver caused the replacement of some of the liver parenchyma. The obliteration of the finest bile capillaries producing the retention continued during this terminal phase, but not enough functioning liver tissue remained to maintain the formerly increased cholesterol formation. One may object to such an explanation, referring to experiences where the total cholesterol values are always very low in cases of hepatic failure, such as in acute yellow atrophy of the liver and in the last stages of a decompensated portal cirrhosis. This



patient, however, never had hepatic failure nor hepatic coma but died as a result of tuberculosis of the lung and disseminated tuberculosis.

3. The cholesterol and lecithin level in the serum in complete obstruction of the common bile duct, resulting from occlusion by a stone, carcinoma or fibrosis after a surgical accident, is never as extremely high as in xanthomatous biliary cirrhosis, that is, values as high as 1450 mg. per cent total cholesterol and 2120 mg. per cent lecithin observed in Mrs. L. M. and in the first stages of other cases of xanthomatous biliary cirrhosis in this paper. The early liver biopsy of Mrs. L. M. showed obliterative changes in the finest bile capillaries in some areas of the liver. It seems, however, unlikely that the fibrotic obliteration of some cholangiololes in parts of the liver at the beginning of the disease should result in a much greater retention of cholesterol and lecithin than is observed in a case with complete occlusion of the common bile duct.<sup>25</sup> With regard to Mrs. L. M., bile was certainly always produced, and that a fair amount reached the intestines was demonstrated by the presence of urobilin and urobilinogen in the feces and urine during the course of the disease and by the aspiration of dye-stained bile from the patient's common duct during the operation. As the disease progresses, the fibrotic changes of the cholangiololes involve greater areas of the periportal space. Thus the retention of bile is certainly increased, but the cholesterol and lecithin values in the serum decrease the more the liver parenchyma is replaced by fibrotic tissue. It may also be noted that the bilirubin values in the serum at the outset were never outstandingly high and definitely not as elevated as those observed in complete blocking of the common duct. The level of bilirubin in the serum of these patients does not parallel the increase or decrease of cholesterol and lecithin.

4. Skin xanthomas were already developed in this case in the early stages of the disease (first year) at a time when the bilirubin was only moderately increased. As far as can be ascertained from the history of the patient, skin xanthomas did not precede the jaundice. Patients with complete obstruction of the common bile duct by stone, carcinoma or surgical obliteration exhibit a severe grade of jaundice, a moderate increase of cholesterol and a slight increase of lecithin, but skin xanthomas do not appear.<sup>25, 26</sup> The rare instances of skin xanthoma reported<sup>18</sup> after surgical obstruction seem rather exceptional. In these cases the skin xanthoma disappeared as soon as the bile flow was restored whereas in xanthomatous biliary cirrhosis, the skin xanthomas persist despite the fact that bile is constantly excreted in the intestines.

The clinical and laboratory data collected during the period of observation favor the suggestion of Thannhauser<sup>24, 27</sup> that the marked accumulation of cholesterol and lecithin at the beginning of xanthomatous biliary cirrhosis is probably not only the result of a retention of bile but also the consequence of an imbalance of increased cholesterol and lecithin production and an inadequate excretion of these substances. The explanation of the finding of excessively high cholesterol and lecithin as the result of hyperproduction of

cholesterol and lecithin in xanthomatous biliary cirrhosis remains a hypothesis. Such a hypothesis is, however, supported by the laboratory findings and by a comparison of this and other cases of xanthomatous biliary cirrhosis with other clinical syndromes where the obstruction and bile retention are complete and the only etiological factor. In the cases of complete obstruction the lecithin and cholesterol content of the serum is by far not as high as in xanthomatous biliary cirrhosis despite the fact that in this disease the bile flow is always patent.

*Case 2.* T. P., 38 year old female, of Finnish descent.

*Past History:* Patient is married and has two children. She was always well until she had menstrual disturbances in January 1938 when she was operated on for a fibroma. After leaving the hospital in February, she felt an itching all over her body. One week later she had attacks of abdominal pain and noticed that her skin was jaundiced. She did nothing until May 1938 when she saw a doctor for her jaundice, which has never since completely cleared. Her appetite was good. She never had chills or fever.

*First Admission* to the Massachusetts General Hospital, Boston, March 20, 1940. Jaundiced patient with no complaints. Heart: Normal in size, no murmur. Blood pressure 108 mm. Hg systolic and 79 mm. diastolic. Liver enlarged, spleen not felt. Laboratory findings: Bilirubin 6.9 biphasic reaction. Prothrombin time 29.1 (normal 21.0). Hinton test negative. Discharged to the out-patient department with the diagnosis, "Biliary cirrhosis" and jaundice. Transferred to Surgical Department, May 19, 1940. Physical examination showed the same findings of an enlarged liver and chronic jaundice. The patient was also seen at the dental clinic for dental bleeding. Laboratory findings: Bromsulfalein test 80 per cent retention. Non-protein nitrogen 18 mg. per cent. Total protein 7.1 gm. Bilirubin: van den Bergh test 13.0 mg. biphasic.

*Exploratory Laparotomy* May 29, 1940 (Dr. A. W. Allen). No fluid in the abdomen. Spleen was three times larger than normal. Liver moderately enlarged. Surface not scarred or nodular but slightly greener than normal. Head of the pancreas normal, but the pancreas was thickened. Bile duct was identified. The common duct was probed. No stones found above and below or toward the gall-bladder. Dark bile could be seen coming from the gall-bladder. No stones. Bile duct roughly 7 mm. in diameter. Comment: After careful exploration no evidence of stone in the duct or gall-bladder.

*Liver Biopsy.* (See page 139.)

*Second Admission:* Had pain on her left side, no loss of weight. Flank pain on both sides. Jaundiced yellow sclerae. Bleeds from the gums very easily. Some brown pigmentation on her face and abdomen. Laboratory findings: Non-protein nitrogen 29 mg. Total protein 5.8 gm. Bilirubin 9.7. Biopsy of skin: No evidence of hemochromatosis.

Patient was seen in the out-patient department and was constantly jaundiced. Bilirubin 28.5 biphasic. Prothrombin time 19. Sodium 139.7 mg. per cent.

*Third Admission, March 1941.* Between January and March 1941 innumerable xanthomas developed on the patient's face, arms, elbows, legs and feet. The creases of the palms showed many flat xanthomatous lesions, firm and yellow, linear and rounded in character.

Roentgen-ray of the esophagus and stomach did not reveal esophageal varices. Prothrombin time taken several times was normal.

Patient was now in the out-patient department repeatedly. The clinical picture did not change.

*Fourth Admission, May 1941.* The patient was hospitalized because of an acute cellulitis of the left leg. After she recovered, one of us was allowed to see her (Thannhauser) through the courtesy of Dr. James H. Means and to examine the serum for the various lipids. The skin, especially around the neck, was dark brownish. The jaundice was of moderate grade. Liver was four fingers below the costal margin. The spleen was large and firm. There was no ascites. Plain xanthomas were noticed around the eyelids and both creases of the hands. The tuberous form of xanthoma, firm and of a yellow carotene color, appeared on her face, neck, elbows, lower arms and legs. Laboratory findings: Van den Bergh 7.9 direct; 9.6 indirect. Lipid partition (see below). (Figure 9.)



FIG. 9. Case 2. T. P. Diffuse brownish pigmentation. Jaundice. Xanthelasma of the eyelids. Tuberous xanthomas of face and neck. Xanthomatous involvement of the creases of both hands.

*Fifth Admission, April 1944.* Patient admitted with bleeding from esophageal varices. No history of alcohol intake. The past few months the patient had felt exhausted but did her housework. About two weeks before her admission the stools became tarry. The day before admission she had a peculiar sensation below the sternum and vomited a tablespoon of bright blood. Her general appearance was the same as previously. The liver and spleen were enlarged. No ascites. Laboratory findings: Non protein nitrogen 35. Bilirubin 6.6 direct; 9.3 indirect. Total serum protein 5.3 gm. Albumin 2.7. Globulin 2.5 (April 5, 1944). Hemoglobin 3.5 gm. Red blood cells 1,500,000. White blood cells 12,200. Polymorphonuclears 84 per cent. Small lymphocytes 9 per cent. Monocytes 0. Platelets decreased (April 22, 1944). Hemoglobin 49 per cent. Red blood cells 3,200,000. Stool: guaiac ++++.

*Sixth Admission, Dec. 16, 1944.* Esophageal bleeding. General appearance unchanged. Laboratory findings. Hemoglobin 5.0 gm. Red blood cells 2,200,000. Polymorphonuclears 90 per cent, lymphocytes 6 per cent, monocytes 2 per cent. Urine, specific gravity 1.106. Albumin +, bile ++++. No tyrosine or leucine crystals. Patient died December 18, 1944.



TABLE II  
Lipid Analysis of the Serum of Patient, T. P.  
The serum is *transparent* and not milky

	May 12, 1941 Analysis— Research Laboratory Boston Dispensary	April 5, 1944 Analysis— Mass. General Hospital	Normal
Total cholesterol	1115 mg. %	368 mg. %	150–260 mg. %
Free cholesterol	143 mg. %		40–70 mg. %
Cholesterol present as esters	972 mg. % (87% of total cholesterol)	110 mg. % (29% of total cholesterol)	70–75 mg. % of total cholesterol
Total phospholipids	2240 mg. %		150–260 mg. %
Cephalin	50		
Lecithin	1710	625	
Serum lipase	Normal		
Diastase	Normal		
Acid phosphatase	Normal		
Alkaline phosphatase	27.5 Bod. U		

Analysis of Liver Tissue after Autopsy, Dec. 19, 1944

		Normal % of dry weight
Total cholesterol	2.2%	2.0 –2.6%
Free cholesterol	1.07%	0.44–0.55%
Cholesterol present as esters	0.13%	1.5 –2.15%
Total phospholipids	7.0%	9.0 –11.0%
Cephalin	5.2%	3.0 –5.5%
Lecithin	1.8%	3.0 –6.0%
Total fatty acids	13.25%	8.6 –13.0%

*Pathological Report:* The biopsy specimen from the liver May 29, 1940 of this patient showed a subacute to chronic inflammatory reaction in every portal area. In addition there was severe bile stasis within the lobules. The inflammatory reaction was confined to widened but well demarcated portal areas. Junction ducts were numerous, but small bile ducts, in contrast, were difficult to find. Neither bile nor leukocytes were seen within any of the bile duct lumina. Liver cells bordering the portal areas showed regressive changes. No xanthoma cells were found in any of the portal areas.

The histological findings at the time of the autopsy, December 18, 1944, were quite different. The uniform distribution of the early inflammatory lesions was replaced by a very patchy disorderly and far advanced perilobular fibrosis. There was little cellular exudate and in these wide communicating bands of fibrous tissue there were very few small insignificant collapsed empty bile ducts. In some areas whole lobules had been destroyed and in other areas the structure of the original lobules was little changed. There was a diffuse and severe bile stasis, most marked in distended canaliculi bordering zones of fibrosis. An interesting finding was the accumulation in some of the dilated sinuses of endothelial cells containing lipoid, but it must be emphasized that no xanthoma cells were found in any of the bile ducts. Scattered throughout the liver and complicating this picture of fibrosis were small nodules of regenerated liver tissue.

The diagnosis of the biopsy specimen was that of chronic pericholangiolitis with beginning pericholangiolitic biliary cirrhosis. The diagnosis of the liver at the time of autopsy was difficult and an accurate interpretation of the pathogenesis of this type of cirrhosis without the earlier biopsy would have been extremely hazardous.

*Clinical Comment:* Patient T. P. presented the following picture during the course of the disease: (1) Continuous jaundice (five years); (2) skin xanthoma (plain and tuberous type for three years); (3) enlarged liver and spleen; (4) extremely high total cholesterol as well as lecithin values in the serum (1115 mg. per cent for total cholesterol and 1710 mg. per cent for lecithin); (5) transparent serum despite the high cholesterol and lecithin content. These features correspond with those of xanthomatous biliary cirrhosis. In the last phase of the patient's illness the values for total cholesterol as well as for lecithin decreased, probably because of the progressing cirrhosis which also produced portal obstruction. Varicose veins of the lower esophagus caused considerable bleeding and led to her death. It is evident from the exploratory laparotomy and from the liver biopsy four years previously that the disease did not start with extensive changes of the liver parenchyma nor with obstruction of the common bile duct. After an insidious onset, jaundice of moderate grade was the first symptom lasting the entire five years of illness. Skin xanthomas were noticed by the patient subsequently two years later. The skin xanthomas persisted even in the final stages although the cholesterol values of the serum decreased considerably because of the progressing cirrhosis. It may, however, be noted that the concentration of cholesterol and lecithin in the serum remained higher than normal until the patient's death.

*Case 3.* Mrs. P. H., 48 year old housewife, was referred by Dr. Edward S. Medoff to the J. H. Pratt Diagnostic Hospital on April 27, 1941.

*Chief Complaint:* Skin trouble and jaundice.

*Present Illness:* Seven or eight years ago this woman first noted the occurrence of dermatographia. If she marked her skin with a match, as in making initials, the contacted area became red and raised, lasted for several minutes and disappeared.

In the fall of 1937 she noticed the onset of weight loss and had a generalized tired feeling. After moderate exercise she felt all in and had no strength. Weight loss of about two pounds a week continued. When these symptoms first appeared, she weighed approximately 134 pounds and within a period of several months, she lost 30 to 40 pounds. In January and February of 1938, she felt a generalized itching, so marked and distressing that she visited a doctor in March. The physician, who had known her for a long time, was surprised to see her yellow skin and told her she had jaundice. A Wassermann test was negative. She now had become quite nervous and irritable. Since she received no relief from the physician's medication, she saw another doctor (1938). At this time she noticed raised areas on the palmar surfaces of both hands. Small nodules appeared in the crevices of the skin and at the flexion point of the fingers, gradually involving the entire hand. The hands were quite swollen, and she was unable to clench her fist. The raised areas were smooth, white at the beginning but later turning yellow. These persisted and about 1939 similar lesions became visible around the eyes and then seemed to spread everywhere. These smooth, raised yellowish-orange lesions were observed around the nose and the neck as far down as the collar bone. They covered the elbows as well as the flexor surface of the forearm, the anterior aspect of the knees, the posterior aspect of the ankles, the skin over the Achilles tendon, and the toes and hands. The rectum and the buttocks also showed these nodules. For about two years there was no particular increase or change in their aspect. However, if the patient happened to scratch one of them severely, it bled and exuded a yellowish fatty material for a short time.

There had been no marked change in the past year or two in the loss of weight, weakness, nervousness and continuous jaundice. In November 1940 the patient had four teeth removed with profuse gum bleeding. In December 1940 her physician did not advise a blood transfusion for the anemia incurred from the blood loss but gave her instead iron pills by mouth, which, according to the patient, had rebuilt her blood.

In the past four months her complexion had become much darker. Within the last two months blister-like lesions had developed over the face, nose and legs. Her weight was now 83 pounds in contrast to 91 pounds the previous year. Her appetite remained good. Sometimes she had considerable abdominal distention with eructations of gas, but this had been noted for a number of years. She had had no other pain or discoloration of the skin prior to her present illness. Since the itching was now quite marked and the skin deeply pigmented, she entered the hospital for further diagnostic studies.



FIG. 10. Case 3. P. H. Severe jaundice. Plain xanthomas (xanthelasma) around both eyes. Plain xanthomas in the supraclavicular fossae. Tuberous xanthomas of the face and neck.

*Family History:* The patient's father had died at the age of 78 of a shock; her mother at 72 of pneumonia. Her mother had had 16 pregnancies. Two were still-born, and eight other children died in infancy. The patient has two brothers and three sisters living and well, none of whom have exhibited any disease or skin dis-

coloration like those of the patient. There was no history of tuberculosis, cancer, diabetes, cardiac or renal disease.

*Marital History:* Married twice, the first time 27 years previously. After eight years, her husband was killed in an automobile accident. They had one child, a boy, now 26 years old. She married a second time 17 years ago; her present husband, a sheet metal worker, is living and well.

*Personal History:* She was born in New Hampshire. Her work had always been of a domestic nature. Habits have been good. Diet adequate. As a result of her present illness the patient was advised to decrease her fat intake, but she still ate a little butter.

*Past History:* General health has always been excellent. The patient has had the usual childhood diseases with no past sequelae. She stated that she is said to have had malaria at the age of eight and remembers having shaking chills then. Has had no operations and no serious injuries.

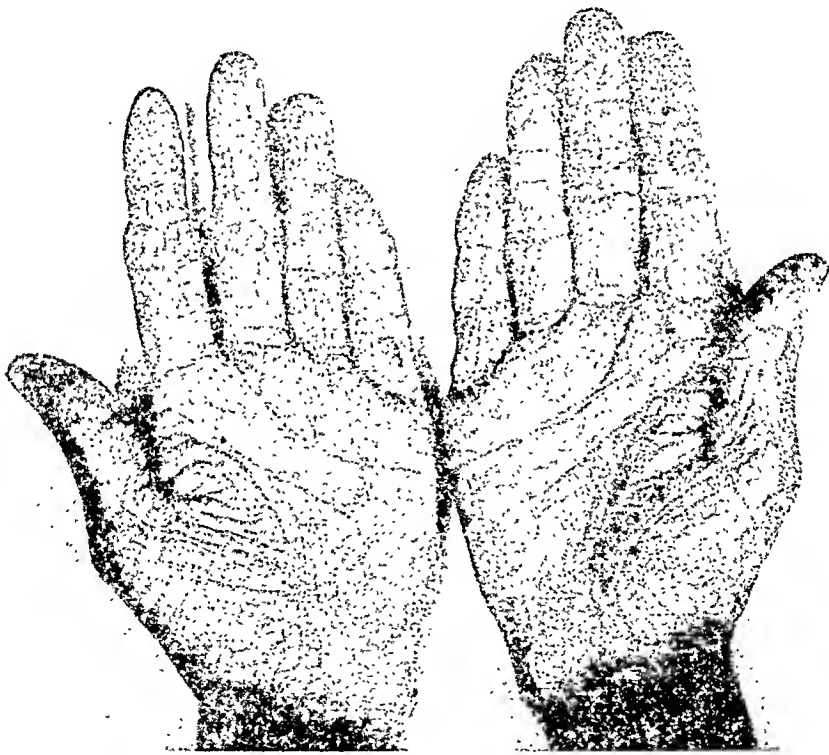


FIG. 11. Case 3. P. H. Plain and tuberous xanthomas of both palms in addition to the xanthomatous involvement of the creases.

*Systemic Review:* Head—no headaches. Her teeth have been bad for a number of years, at least eight or ten. Her gums bleed quite easily, more noticeably so during the last few years. Her vision has been good. She has had no difficulty in hearing, no earaches. No glandular swelling of the neck. Cardiorespiratory: No substernal pain, precordial distress. In the winter time she has a cough. Gastrointestinal: Appetite has always been good. Bowel movements fairly regular. She takes a laxative occasionally. In the past two years her stools have been of different colors—at times black as tar or yellow, and sometimes yellow streaked or brown. She states that the stools are very greasy “as if you had thrown in a cup of grease.” In the

past two weeks she has felt a slightly irritated area posterior to the rectum, especially when sitting on a hard chair. Genitourinary: Patient has always drunk much water and voids extensively. Since the presence of the jaundice, the color of the urine has been quite brown. No dysuria, pyuria, or pain simulating renal colic. Menstrual: Until onset of the present illness periods were quite regular but are no longer so. The last period was one month ago, and the previous one five months prior to that. The amount of flow has been decreased during the past two years. Sometimes she has clots. No dysmenorrhea. Skeletal: For the past two years she has had difficulty in kneeling, that is, pain in the knees on marked flexion. She knows of no swelling of the painful joints. Allergy: No manifestation. Diet: During the past two to three years the patient has been trying to decrease the amount of fat intake.

*Physical Examination:* On admission, temperature 98.6°. Pulse 80. Respirations 20. Weight 83½ pounds. Height 5 feet 4 inches.



FIG. 12. Case 3. P. H. Tuberous xanthomas on elbows and trunk.

The patient is a slight middle-aged woman, who appears much older than her years. She is mentally alert and quite jolly. The skin is deeply yellow and pigmented. The pigmentation is much deeper over the chest and abdomen. Another striking finding is the conspicuous xanthomatous lesions of the skin. These lesions include extensive xanthelasma, quite smooth and yellow-orange in color, around the eyes, involving the upper lids more extensively than the lower ones. Several single papillar lesions, slightly yellow in color are found on the face as well as inside the nasal cavities bilaterally. On the lateral aspect of the neck, at the collar bone, are two (bilateral) areas of smooth slightly raised xanthomatous deposits (xanthoma plana).

Similar xanthomatous lesions appear on each flexor aspect of the forearm. Along the elbow are raised tuberos lesions which are nodular and easily moved about. Extensive nodular xanthomatous lesions cover the palmar surface of both hands. The inferior aspect of both breasts at the points of approximation to the thorax show a linear deposition of xanthomatous material. On the anterior aspect of the knee are tuberos xanthomatous lesions, also similar ones between the toes, and several on the dorsum of the feet. Numerous tuberos xanthoma also occur on the knuckles of the hands, the region of the heel, and on the skin over the Achilles tendon. Widely dis-



FIG. 13. *Case 3.* Tuberos xanthomas of the patellas and lower legs.

persed xanthomatous nodules are found over the buttocks and there is a band of xanthomatous tissue around the anal orifice. There are also tiny single, yellowish, smooth areas over the back and occasional xanthomatous nodules over the entire body. There is marked icterus of the sclerae and the buccal membrane including the pharynx. As already mentioned, the skin is deeply jaundiced everywhere. The hair on the head is plentiful but graying. Eyes show no undue prominence. Pupils are of moderate size and round. The left pupil is somewhat larger than the right but both react well to light and to accommodation. Extraocular movements well carried out. No nystagmus.

The fundi show the discs to be well outlined as are the retinal arteries and veins. There is a suggestive yellowish tinge to the fundi. No hemorrhages or exudates noted. Nose: In the right nares there is a projection, but it cannot be said yet whether it arises from the septum or from the concha. No bleeding points of the mucous membranes were observed. Mouth: The tongue protrudes in midline without tremor, is slightly coated and fairly well papillated. Lower teeth are dirty and carious; several upper ones have been removed. The pharynx is icteric. Tonsils are small. No post-nasal discharge. Ears: The hearing is good. No mastoid tenderness. Sinuses: There is no tenderness over the maxillary sinuses. Neck: No glandular enlargement, neither is there generalized glandular enlargement. Thyroid: Not enlarged. Trachea in midline. Chest: The breasts are soft, no nodules, no tenderness. Lungs: Expansion good and equal on deep percussion. Lungs resonant throughout. On auscultation no râles are heard. Breath sounds are vesicular. Heart not enlarged, left border dullness being 8 cm. from the midline in the left fifth interspace. Heart sounds are loudest at the fourth interspace just lateral to the border of the sternum. Heart rhythm is regular. Blood pressure 160/80 in the right arm. Radial pulse regular and equal. Abdomen: Rather protuberant. The patient states that her umbilicus is now somewhat firm, this being unusual; she also thinks that the configuration has changed in the past year or two. In the left upper quadrant is a small mass which on palpation is found to be a firm spleen, extending a hand's breadth below the costal margin. The liver is easily palpable, firm, non-tender, and also extends one hand's breadth below the costal margin in the mid-clavicular line. No other masses are felt. No tenderness. Extremities: no cyanosis of the nail bed; no ankle edema. Skeletal: No pain or limitation in movement of any of the joints except the knee joints. Patient cannot flex the left shank on the thigh, the angle of limitation being approximately 45 degrees. No swelling, no tenderness or increased heat in any of the joints. The patient also cannot completely flex the fingers because of the xanthomatous lesions. Neurological: Cranial nerves are intact. No motor or sensory disturbances. Reflexes are active and equal.

*Laboratory Data:* Urine, on admission, amber color, very slightly cloudy, alkaline reaction, specific gravity 1.009, slight trace of albumin, no sugar or urobilin, normal urobilinogen. Bile showed a three plus reaction. Sediment showed 1 to 3 red cells per high power field, less than one leukocyte per high power field. Scattered epithelial cells, many bacteria; one small clump of pus was seen.

*Blood on admission:* 71 per cent hemoglobin, 3.69 million red blood cells with color index of 0.96. White blood count 9,400 with 15 bands, 60 polymorphonuclears, 2 eosinophiles, 3 basophiles, 16 lymphocytes, 4 monocytes. Smear showed much anisocytosis, platelets appeared normal. Blood fragility tests: Control: hemolysis began at 0.42, it was complete at 0.32; the patient's hemolysis began at 0.40 and was complete at 0.24. Supernatant fluid of first tubes was yellow due to bilirubin; checked with serum in saline, plus water, gave the same color. (For analysis of the serum for lipids, see table 3.) Icteric index of 150; bilirubin, direct 15.9 mg. per cent; indirect 20.4 mg. per cent. Fasting blood sugar examination was 100 mg. per cent. The bromsulfalein liver function test, using 5 mg. per kilogram of body weight, showed over 50 per cent retention in one-half hour and 50 per cent retention in one hour. Blood sedimentation rate was 18 mm. in 20 minutes, 66 mm. in one hour, and 112 mm. in two hours by the Westergren method. Serology: Hinton, Wassermann and Kahn tests negative. Blood lipase: 0.48 c.c. of .05 normal potassium hydroxide per 1 c.c. of serum (lower limit value for lipase in serum of normal individuals). Prothrombin time, 35 seconds; normal control, 20 to 25 seconds.

*Roentgen-ray Examinations:* The following roentgenologic studies were done by Dr. Alice Ettinger: *Oral Graham test:* "Fourteen hours after double oral dye no distinct gall-bladder shadow can be recognized in the right half of the abdomen, which

can be considered to represent the gall-bladder. There is also no shadow after a fatty meal. Diagnosis: In the presence of jaundice, the lack of filling of the gall-bladder cannot be properly evaluated as to the presence of gall-bladder disease." *G. I. Series*: "Smooth passage of the barium through the esophagus. Slight herniation of the stomach mucosa above the diaphragm. Normal relief; regular curvatures. The stomach is slightly displaced to the right by an enlarged spleen. Nothing unusual in the upper loops of the small intestines. Diagnosis: No x-ray evidence of varices or any pathological lesion of the stomach, duodenum, and upper loops of the small intestines." *X-ray of the long bones and of the skull*: "There is no x-ray evidence of any bone changes." *X-ray of the chest*: "Both diaphragms are smooth in outline with clear angles. The lung fields are free from infiltration. The heart is normal in size and shape." Diagnosis: "There is no x-ray evidence of a pathological lesion of the chest."

*Hospital Course*: During the seven-day hospital stay the patient had no particular complaints. Request for a sternal puncture and peritoneoscopy as well as the gynecological examination was refused.

Patient was seen ambulatorily on May 29, 1941. She complained only about the itching of the skin. She claimed she kept her diet free of animal cholesterol and fat. She did her housework and even went out dancing several times. Physical findings were unchanged since her hospital admission. Liver and spleen were enlarged. No attacks of pain or fever. No ascites. No edema of the legs. (For analysis of serum lipids, see table 3.) Bilirubin: direct 12; indirect 16.

The patient was uncoöperative and did not appear for another examination. Dr. E. B. Medoff, Woonsocket, R. I., reported that Mrs. P. H. died February 1943 "a rather slow lingering death accompanied by numerous hemorrhages from the gums, mouth, rectum and frequent vomiting of blood. An autopsy was denied."

TABLE III  
Lipid Analysis of the Serum of Mrs. P. H.  
The serum was transparent and not milky

	April 28, 1941	May 29, 1941	Normal
Total cholesterol	1535 mg. %	1140 mg. %	150-260 mg. %
Free cholesterol	275 mg. %	320 mg. %	40-70 mg. %
Cholesterol present as esters	1260 mg. % (82% of total cholesterol)	910 mg. % (79% of total cholesterol)	70-75% of total cholesterol

*Clinical Comment*: Patient P. H. exhibited the most extensive involvement of the skin with xanthomatous lesions in our experience (figures 10, 11, 12, 13). Since she was uncoöperative toward the end, the clinical and laboratory follow-up studies in the final two years of her life are incomplete. It is evident from the report of the attending physician that her death was caused by bleeding from esophageal varices due to progressing cirrhosis, which finally also resulted in portal obstruction. It is noteworthy that at the height of her disease, during the period of clinical observation, the cholesterol esters were neither diminished nor were signs of portal congestion like esophageal varices present. As in the case of T. P. the symptoms of portal obstruction occurred in the last phase of her illness, but these features have no relation to the early manifestations of the disease. In other words, the histological demonstration of severe cirrhosis in the end stages of a case of xanthomatous



biliary cirrhosis should not be taken as a sign that skin xanthomas and chronic obstructive jaundice are complications of the common type of portal cirrhosis; rather the reverse sequence of events seems to occur. For years the fibrotic changes are localized around the finest ramifications of the bile capillaries and junction ducts producing the characteristic histological picture of pericholangiolitic biliary cirrhosis. In the last phases, however, the symptoms of portal congestion may develop and lead to the fatal outcome.

*Case 4.* This case published by Eusterman and Montgomery<sup>18</sup> is included in this report because one of us (MacMahon) through the courtesy of S. Warren Hunter, Department of Pathology, University of Ohio, studied the histology of the liver. The complete case history is found in the original paper. The patient, a 48 year old female, noticed in 1940 a "rash" of wide distribution. This eruption consisted of recurrent pruritic lesions, some of which the patient described as having a central plug without pustulation. (This type of papulo-pustular eruption has been described by Thannhauser and Magendantz in similar cases.) Yellow tuberous xanthomas had persisted and progressed since December 1940. Two years previously the liver was found to be enlarged. Jaundice was first observed in October 1940, eight months prior to the patient's admission. She had lost 40 pounds. The family history was without significance. The patient had abused alcohol for 10 years. There was no history of biliary colic or acholic stools.

Physical examination disclosed the presence of icterus, anemia and generalized xanthoma. Yellow nodules, 1 to 3 mm. in diameter, were present on the buttocks, lower part of the back, upper part of the thigh, elbows and both cheeks. Nodules and infiltrated plaques were found on the extensor surfaces of the legs, Achilles tendon and eyelids. In addition there were yellowish infiltrations covering the creases of the palms as well as discrete nodules on both the palms and soles. The liver was firm, insensitive and not especially nodular. However, it was considerably enlarged, the lower border extending one inch above the umbilicus. The spleen could not be palpated, and there was no evidence of the presence of ascites then or subsequently. Although the feces were normal in color, biliuria, grade I, was present. (Death occurred about one year later in California in August 1942 as a result of a massive terminal gastrointestinal hemorrhage.)

*Laboratory Findings:* Serum bilirubin was 5 mg. per cent and the van den Bergh reaction was direct. The hippuric acid test was normal. The albumin-globulin ratio was 1.1:1. The prothrombin time was within normal limits.

TABLE IV  
Values for Plasma Lipids mg. per 100 c.c.  
G. B. Eusterman and H. Montgomery

	March 24/41	May 17/41	May 26/41	July 8/41	July 25/41	Sept. 12/41	Dec. 11/41	April 15/42
Total cholesterol	1320	1388	1388	1193	926	820	1155	352
Cholesterol present as esters		666	980	374	443	625		
Lecithin		2592	1668	1087	1800	1330	1000	555
Total fatty acids		2107	1669	808	2240	800	620	
Neutral fat*		Neg.	Neg.	Neg.	Neg.	Neg.		

\* The values for neutral fat were not charted in the paper of Eusterman and Montgomery but calculated by us according to the formula of Thannhauser and Reinstein<sup>47</sup> by subtracting the sum of the fatty acids present as cholesterol esters and glycerol esters present in the lecithin from the figures tabulated for total fatty acids.

One of the characteristics of the syndrome of xanthomatous biliary cirrhosis, according to Thannhauser and Magendantz, is the transparency of the serum despite the accumulation of cholesterol and lecithin, a fact explained by the normal or mostly low neutral fat content of the serum. In Eusterman and Montgomery's case excessive hypercholesteremia and hyperlecithemia were present, but low, in fact, negative values for neutral fat can be calculated from these figures. It may therefore be surmised that the serum of the patient was transparent and not creamy. The term hyperlipemia, as Thannhauser<sup>27</sup> pointed out, should be used to signify only the accumulation of neutral fat while hypercholesteremia and hyperlecithemia of an extremely high grade may occur without hyperlipemia. This phenomenon of an extremely high cholesterol and lecithin content of the serum together with a low value for neutral fat, considered as characteristic of xanthomatous biliary cirrhosis, was also observed in the above case.

*Pathology.* A block of liver tissue removed at the time of the autopsy was very kindly sent on to us for study. The picture was one of a very advanced cirrhosis and, except for two minute fields, there was no evidence of an active inflammatory process. Large communicating bands of fibrous tissue containing few collapsed and compressed minute bile ducts divided the liver into nodules and lobules. In some of these nodules the parenchyma was well preserved and healthy central veins were easily discernible. In others, there were only nodules of liver cells and sinuses. It is important to note that the nodules and lobules of liver tissue were free of intralobular fibrosis. The pathological changes were so far advanced and the inflammatory reaction had so nearly healed that it was hazardous to guess what this liver was like in its earliest stages. The fact that the fibrosis was centered in the portal areas, and that many lobules with their central veins were still preserved strongly suggested that we were dealing here with a type of biliary cirrhosis, but it was impossible to say in so late a lesion whether it began as a cholangiolitic or pericholangiolitic process. It is important to note that, as in the other cases, no xanthoma cells were found in any of the bile ducts.

*Case 5.* A 46 year old married, white female entered the Evans Memorial Hospital, Boston, on August 19, 1943. Her chief complaint was jaundice of 16 months' duration.

*Past History:* In childhood the patient had had scarlet fever and diphtheria. Subsequently she had always been well until the onset of her present illness. She had, however, always been thin, her best weight having been 108 pounds. There was no history of typhoid, exposure to toxic chemicals or alcohol ingestion. Except for mild and transient bouts of diarrhea, there had been no specific gastrointestinal disturbances.

*Present Illness:* In January 1942 the patient began to feel weak and run-down but had no localized symptoms. Her friends and physician told her that she was quite jaundiced. Subsequently her stools became light, her urine dark, and her skin itchy; a dragging sensation developed in the right upper quadrant.

Since she obtained no relief from a low-fat diet, her physician sent her to the Pondville Hospital and told her she might have a "growth." On June 8, 1942 an exploratory laparotomy revealed no obstruction in the extra-hepatic biliary tract. A biopsy of the liver was obtained. A retrograde cholangiogram made after the operation showed no evidence of biliary tract obstruction.

Following her discharge from the Pondville Hospital, the patient weighed 88 pounds. Many excoriations developed on her skin in May 1942, some becoming secondarily infected. The excoriations bled easily, and there were several episodes of

epistaxis. The jaundice remained about the same. Anorexia was quite prominent, but there were no other gastrointestinal symptoms.

In March 1943 yellow plaques appeared on the margins of both upper lids. Subsequently other plaques developed on the flexor folds of her hands and both arms as well as on the back, neck, shoulders, and axillae.

Since the patient failed to show any appreciable change and since the attending physician noted progressive enlargement of her liver, she was admitted to the Evans Memorial for further study. At the time of her first admission the jaundice had already lasted for 16 months. The skin xanthomas had developed about nine months previously.

*Physical Examination:* Revealed a well-developed, moderately emaciated, jaundiced woman appearing older than her stated age, sitting in bed and scratching. Skin, sclerae and buccal membranes were icteric. Numerous xanthomatous plaques were observed in the axillae, on the flexor surfaces of the arms and hands, and on the posterior surfaces of the thorax, and on the eyelids. Several of these were excoriated. The hair follicles over the extensor surfaces of the thighs showed papulo-pustular eruptions. There were no petechiae or spider angiomas. Pupils were reactive. Marked dental caries. One bleeding fungating nodule, 4 mm. in diameter, was noted below the left lower canine tooth. Thyroid was not enlarged. Lungs were clear and resonant. Heart was not enlarged. Rate 60; regular. Blood pressure 150/62. No peripheral sclerosis. Liver palpable four fingers below the right costal margin; firm, nodular and non-tender. Spleen not palpable—slight tenderness in right lower quadrant. Rectal examination revealed no hemorrhoids. Cervix uteri posterior; non-tender. Reflexes hyperactive. Weight 98 pounds.

*Laboratory Data:* Hinton negative. Urine: Color dark brown to dark yellow. Specific gravity ranged from 1.017 to 1.027. Bile 4 + on 13 occasions. Urobilinogen was frequently present as high as 1:64 dilution. Sediment was negative. Red blood count ranged from 4.5 to 2.85 million and hemoglobin from 13 to 10 grams. Prothrombin time on two occasions 90.9 per cent of normal and 100 per cent of normal, respectively. Clotting time 14 minutes and 30 seconds. Bleeding time 3 minutes and 30 seconds. Clotting time, repeated, 15 minutes, and bleeding time, repeated prior to discharge, 3 minutes and 15 seconds. White blood count on admission 9,500 with 70 per cent polymorphonuclears, 25 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophiles. White blood count varied between 6,000 and the admission count with differential essentially the same. Non-protein nitrogen 26 mg. per cent. Total protein on two occasions 7.65 grams per cent and 6.26 grams per cent. Albumin on two occasions 2.97 and 2.38 grams and globulin 4.68 and 3.88 grams with A.G. ratios of 0.63 and 0.61. Icterus indices: 75, 90, 80, 80, 80, 60, 75, 83 and 90. Calcium was 8 mg. per cent. Phosphorus 3.96 mg. per cent. Stools brown, formed and firm. Guaiac negative. Stools were negative for pathological intestinal bacteria on culture. Hippuric acid excreted 1.28 gm. in two hours. (Unable to void in one hour.) Alkaline phosphatase 23 King-Armstrong units. Van den Bergh, qualitative, direct positive; quantitative, 5.23 mg. per cent. (Cholesterol figures, table 5.) Duodenal drainage; A. bile, light yellow; B. bile, light yellow; no crystals or parasites; microscopic: white blood cells and mucus. Carotene and vitamin A in serum; carotene was 20 gamma per cent (normal 100 to 250 gamma per cent). Vitamin A could not be read because of excess and abnormal lipid content. Serum total lipid content (ether extraction) 3.96 gm. per cent. Lipid tolerance test (1 gram fat per kilogram per os), fasting 4.32 gm. per cent; 3 hours 4.43 grams per cent; 5 hours 4.22 grams per cent. Serum lipase 0.64 c.c. NaOH (Normal). *Serum showed no gross lipemia, being quite clear. Chylomicrons were markedly reduced in number.* Three days stool; daily fat intake of 50 grams; weight of stool wet 454 grams; dry 148.5 grams; stool fat 49.6 grams/three days. Alkaline phosphatase repeated was 21 King-Arm-

strong units. Van den Bergh—immediate, biphasic, quantitative 6.75 mg. per cent of bilirubin.

*Roentgen-ray Examination:* Skull—vault not remarkable. No localized areas of erosion or hyperostosis. Vessel markings normal in size and distribution. No abnormality of bone texture noted. Sella turcica normal in size and contour. Pelvis—no evidence of bone pathology. Femora—poorly defined osteolytic areas at the distal end of each femur, not typical of any particular disease; soft tissue mass at the pelvis, probably due to distended bladder. Roentgenogram of the chest showed no evidence of active pulmonary disease.

*Clinical Course:* Patient spent 36 days in the hospital. Temperature showed a constant wide swing although almost always within normal limits except for two or three times when it rose to 100°. Pulse was in conformance with temperature but averaged between 50 and 70 throughout the hospital course. Intake and output were not remarkable. Patient was up and around during her stay, complaining only of intense itching on various occasions. Calcium gluconate was administered, 10 c.c. of 10 per cent solution, with occasional relief from itching. On admission the patient weighed 94 pounds and on discharge weighed approximately 93 pounds. Blood pressure during course averaged about 120/74.

The patient was placed on a low-fat, low-cholesterol diet. She was later given 20 gm. of lecithin t.i.d., as well as vitamins A and B complex and vitamin D. One tablet of desoxycholic acid was also given t.i.d. The patient, however, was unable to take the lecithin adequately.

*Follow-up Notes:* The patient was put on a diet containing 50 gm. of fat with no animal fat allowed. She was advised to eat as many protein rich foods as possible. She was given three tablets of vitamin B complex daily, 45,000 units of vitamin A and 9,000 units of vitamin D daily, and 1 mg. of vitamin K twice a week. Through the kindness of Dr. Lester Dragstedt she was given at first 12 and subsequently 15 capsules of lipocaic daily.

The patient made some improvement on this regimen. Her weight reached 101 pounds as compared to 93 pounds at the time of discharge, and she felt much stronger. On the other hand, the size of her liver did not change appreciably. The skin xanthoma were also unchanged. The laboratory studies showed no clear-cut improvement in the serum carotene, vitamin A and bilirubin content.

*Second Admission:* Red blood cells 1,620,000; hemoglobin 6.2 gm.; white blood cells 15,050. Differential count normal. Hematosis 11 per cent. M.C.V. 73. M.C.V. 36. Clotting time 4½ minutes. Bleeding time 5¼ minutes. During the patient's hospital stay red cell count improved: 3,720,000 red blood cells; 11.0 grams hemoglobin. Stool showed four plus guaiac from fifth to ninth day, two plus on tenth day and zero to one plus thereafter. Total protein 5.25. Albumin 1.94. Globulin 3.31. A.G. ratio 0.59. Roentgen-ray for esophageal varices negative. Cephalin flocculation test ++++.

*Third Admission:* Patient was on a diet low in animal fat and containing vitamin B complex and vitamin K. Jaundice has not increased or decreased although pruritus has been less marked. Two weeks prior to her third admission she had an episode similar to the one which precipitated her second hospital admission—weakness, dizziness, and passage of black stools. Three hours prior to the present admission she had another spell of weakness and passing of tarry stools. After transfusions she recovered but stools remained positive for six days.

*Laboratory Data:* Red blood cells 2,980,000; hemoglobin 7.6 gm.; white blood cells 12,050. Total protein 4.3. Albumin 2.1. Globulin 2.2. Patient was discharged with hemoglobin 12.9 grams, white blood cells 7,800. Cephalin flocculation ++++. Cholesterol analysis, see table 5.

*Fourth Admission:* On the day of admission the patient vomited several times.

Vomitus was of a coffee ground color. Patient was confused and dyspneic. Dyspnea disappeared when she lay down.

*Laboratory Data:* Urine 3+ bile. Hematocrit ranged from 14 to 35 per cent. Hemoglobin ranged from 5 to 5.5 gm.; white blood cells from 26,900 to 6,700 with normal differential count. Non-protein nitrogen 43 mg. per cent. Total protein 5.23. Albumin 2.55. Globulin 2.91. A.G. ratio 1:1. Cephalin flocculation 4+. Stools: guaiac 4+ for five days. For cholesterols, see table 5.

*Fifth Admission:* One week prior to admission the patient passed dark blood per rectum and felt weak. One day prior to admission the patient vomited bright red blood and passed dark blood per rectum. She felt weak and developed a terrible thirst. Temperature 98.6°. Pulse 102. Respirations 20. Skin dusky green-yellow hue. Skin xanthomas did not change from the time of her previous admissions. Light colored plaques ranging from 2 mm. to 3 cm. in diameter. Heart: systolic murmur; blood pressure 94/35.

*Laboratory Data:* Urine bile 9+. B.S.R. 99. Hemoglobin 4.9 gm.; and after 10 blood transfusions 11.5 gm. Prothrombin time 44.2 seconds. Control 20 seconds. Total protein 3.98. Albumin 1.87. Globulin 1.61. Total protein increased finally to 6.25 gm. Non-protein nitrogen 43 mg. Blood sugar 99 mg. per cent. Cholesterol values, see table 5.

*Sixth Admission:* Since her discharge the patient has been followed by Dr. F. Ingelfinger in the Outpatient Department of the Evans Memorial Hospital. For about six months she has had a warty "horn-like" papilloma at the inner canthus of the right eye. Four days prior to her admission following a minor trauma, she bled profusely and has continued to bleed intermittently despite ligation by her local physician. The patient has also noticed occasional bleeding from the gums. Itching was at times very intense. She followed only moderately well a fat-free diet.

Temperature 98.6°. Pulse 68. Small thin female, who appeared chronically ill but in no acute distress. Skin was of deep brownish-yellow color and contained numerous plain and tuberous xanthomas, particularly about the upper trunk and arms. Over the legs were papulo-pustular lesions. Mucous membranes of the mouth were deeply pigmented. Chest was clear to percussion and auscultation. Heart: Point of maximal impulse in the fifth interspace 7 cm. from the midsternal line and except for a grade 3 blowing systolic murmur was otherwise not remarkable. The liver edge was palpable below the level of the iliac crest and in the epigastrium. The liver was smooth and not tender.

*Laboratory Data:* Urine 4+ bilirubin and numerous tyrosin crystals. B.S.R. 108 per hour. Hemoglobin 10.8 gm. White blood cells 9,350. Fasting blood sugar 90 mg. per cent. Total protein 6.6 gm. Albumin 2.88 gm. Globulin 3.69 gm. Prothrombin time 22.4 seconds. (Control 19.8 sec.) Cephalin flocculation 4+. Thymol turbidity 36. Cholesterol and bilirubin, see table 5.

The lesion of the inner canthus of the eye was healed at the time of the patient's discharge. The patient was advised to stay on a high-protein, high-vitamin, high-carbohydrate, but low-fat diet. Arrangements were made to have her receive injections of vitamin K twice a week.

*Pathology.* A laparotomy\* was done at the Pondville Hospital in June of 1942. Exploration revealed no extra-hepatic biliary obstruction.

*Microscopic Examination:* This was an unusually satisfactory section and included approximately 50 lobules. The section was well cut and beautifully stained. There were four serial sections on the one slide, affording an opportunity to follow a lesion from section to section.

\* We are indebted to Dr. Gerald C. Leary, Resident Pathologist at the Pondville Hospital, for permission to study a section of liver and lymph node obtained by biopsy at the time of operation.



The most striking change was a chronic inflammatory reaction in each portal area (figure 14). There was marked bile stasis within the lobules and this was concentrated in the central zones. A third change was the focal accumulation of inflammatory cells in nests within the lobules, and a fourth change was a focal derangement of the trabecular pattern of liver cells within the lobule. In addition to these there

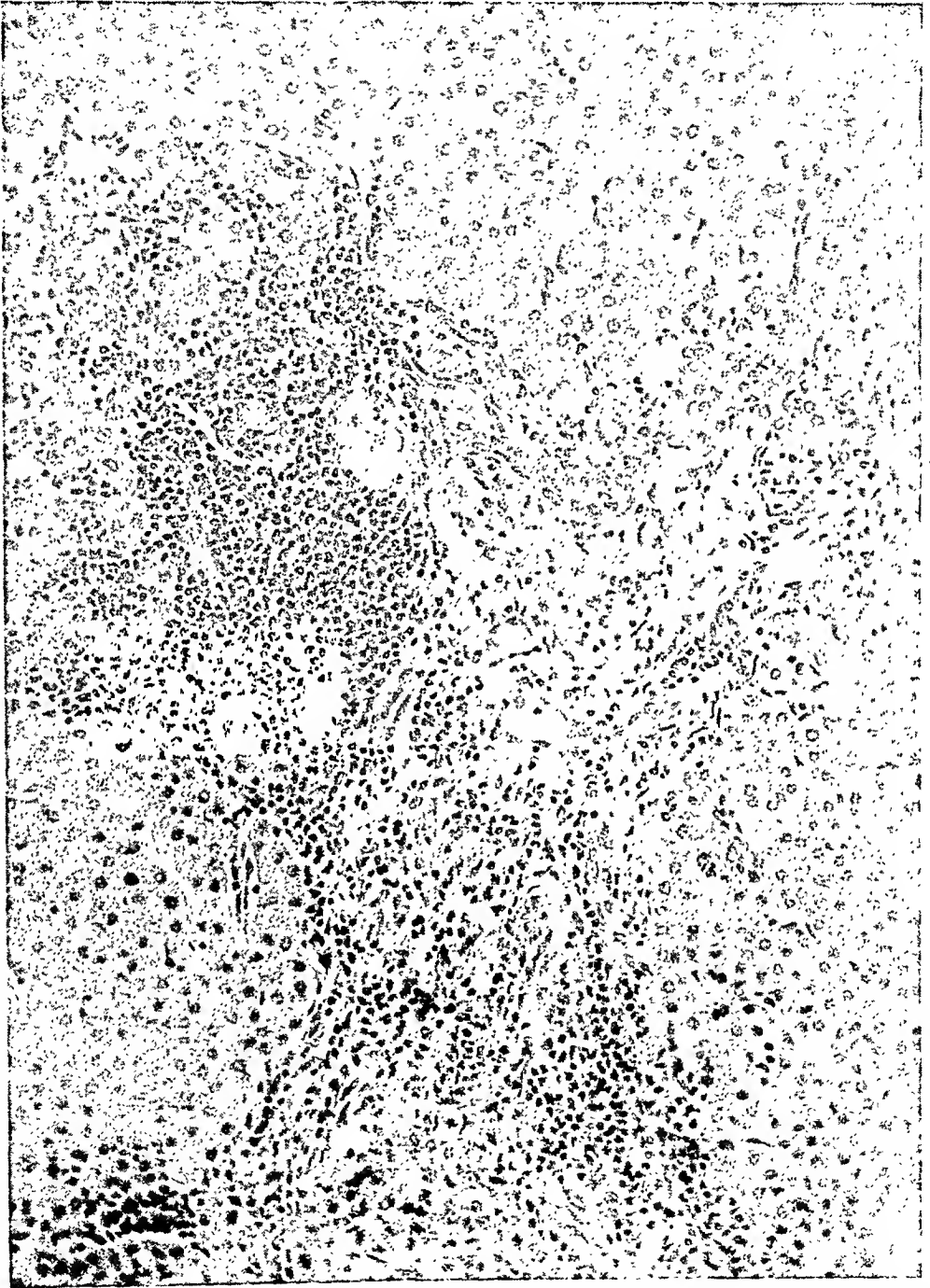


FIG. 14. Liver. This field was selected to show a widened portal area that is the site of a chronic inflammatory reaction. The exudate is dominated by lymphocytes and mononuclear cells. The inflammatory reaction seems to spill over into the adjacent lobule. Small bile ducts are inconspicuous.

was degeneration and necrosis of liver cells singly and in small clusters, but a very careful search failed to reveal a single mitotic figure in either liver cell or bile duct. The sinus endothelium was swollen. Some of the sinuses were dilated, others were compressed. The central veins for the most part were intact and free of abnormalities,



FIG. 15. Liver. This section was selected to show a portal area and the adjoining liver parenchyma. There is a very rich cellular exudate throughout the interstitial tissue. The granulation tissue almost hidden by this cellular exudate, reaches out into the adjoining lobules. Small bile ducts are empty and inconspicuous.



but occasionally a few lymphocytes were clustered in this area. This was particularly true when a band of inflammatory granulation tissue extended deeply into the substance of a lobule.

The oldest and most conspicuous change lay in the portal areas. These zones of connective tissue were larger, broader and in some places exerted an obvious compression effect on the adjacent liver parenchyma. In this biopsy specimen there were medium-sized and terminal portal areas allowing an opportunity to study the inflammatory reaction about the small and larger vessels. The inflammatory reaction was the same in the small and larger portal areas, but it differed in extent from one area to another. The reaction was confined to the interstitial tissue, though there were changes in bile ducts, veins, lymphatics and arteries. This reaction was dominated by a cellular infiltration and by a moderate proliferation of fibroblasts (figure 15). Lymphocytes, plasma cells and mononuclear cells were most numerous. In addition, there were polymorphonuclear leukocytes and a slight scattering of eosinophiles. In one field there was a very well formed lymph follicle. There was nothing specific about the inflammatory reaction and there were no xanthoma cells. The reaction, though diffuse in the portal areas, was most closely associated with the small and terminal bile ducts. No leukocytes were found within these ducts. The reaction extended to the outer margin of the portal area and spread in coarse and narrow extensions into the peripheral zones of the lobules. It blocked sinuses and isolated nests of liver cells.

This extension into the lobule was confined to the outer zones of the lobule, but occasionally, where lobule and central vein were close, it spread from one to the other. Mitoses were found in histiocytes, plasma cells and fibroblasts, but no mitoses were found in bile ducts or liver cells.

The bile ducts were of particular interest; all, large and small, were empty. The large ones were collapsed and the epithelium seemed hyperplastic and almost papillary (figure 16). At no point was the epithelial lining of the larger ducts interrupted. The medium sized ducts and the very small ducts were difficult to find. Those that were visible were intact and empty. Compressed liver cells and junction ducts, which are composed of modified liver cells, were very conspicuous. They turned and twisted and lay embedded in inflammatory granulation tissue. These compressed, twisted and branching ducts suggested at first glance a great increase in small bile ducts. The cells of the junction ducts often showed degeneration, necrosis and leukocytic infiltration. Some of these cells were deeply pigmented with bile. These junction ducts appear to have suffered the greatest injury. None of these cells showed fat vacuoles or hyaline degeneration.

The intralobular bile canaliculi showed the changes of long-standing biliary obstruction. Casts were found throughout the lobules. Some were obviously old and were lamellated (figure 17). There was a very definite intralobular bile stasis. The greatest concentration of bile was in the center of the lobule and in areas adjacent to these bile casts liver cells had undergone degeneration and necrosis.

In summing up the findings in this case, it seems important to point out that the inflammatory reaction was centered in the interstitial connective tissue and that the changes within the lobules were secondary to this inflammatory reaction in the portal area. Because of the location of the lesion, it seems reasonable to consider it as a form of chronic pericholangiolitis, and because there is already beginning cirrhosis, the diagnosis of pericholangiolitic biliary cirrhosis seems acceptable.

A section of lymph node, taken at the time of biopsy, showed three interesting changes. (1) There was a hyperplasia, swelling and accumulation of large mononuclear cells in dilated sinuses. The cytoplasm of these cells was clear and vacuolated, suggesting fat storage. (2) Many of the endothelial cells contained clumps of bile pigment. This clearly showed the effects of an intra-hepatic bile stasis and the extra-



FIG. 16. Liver. This field was selected to show one of the larger bile ducts found in the biopsy specimen. The lumen is empty, the epithelium is well preserved and hyperplastic. The surrounding interstitial tissue is the seat of a chronic inflammatory reaction. No bile and no leukocytes are visible within the lumen.

vasation of bile from the liver into the lymphatics. (3) There were areas of necrosis, calcification and foreign-body giant cell reaction. A fourth finding, though much less significant, was a light eosinophilia throughout the section. In passing, it is interesting to recall that all of these findings in the lymph node may be seen in lymph nodes in cases of simple uncomplicated extra-hepatic bile stasis.

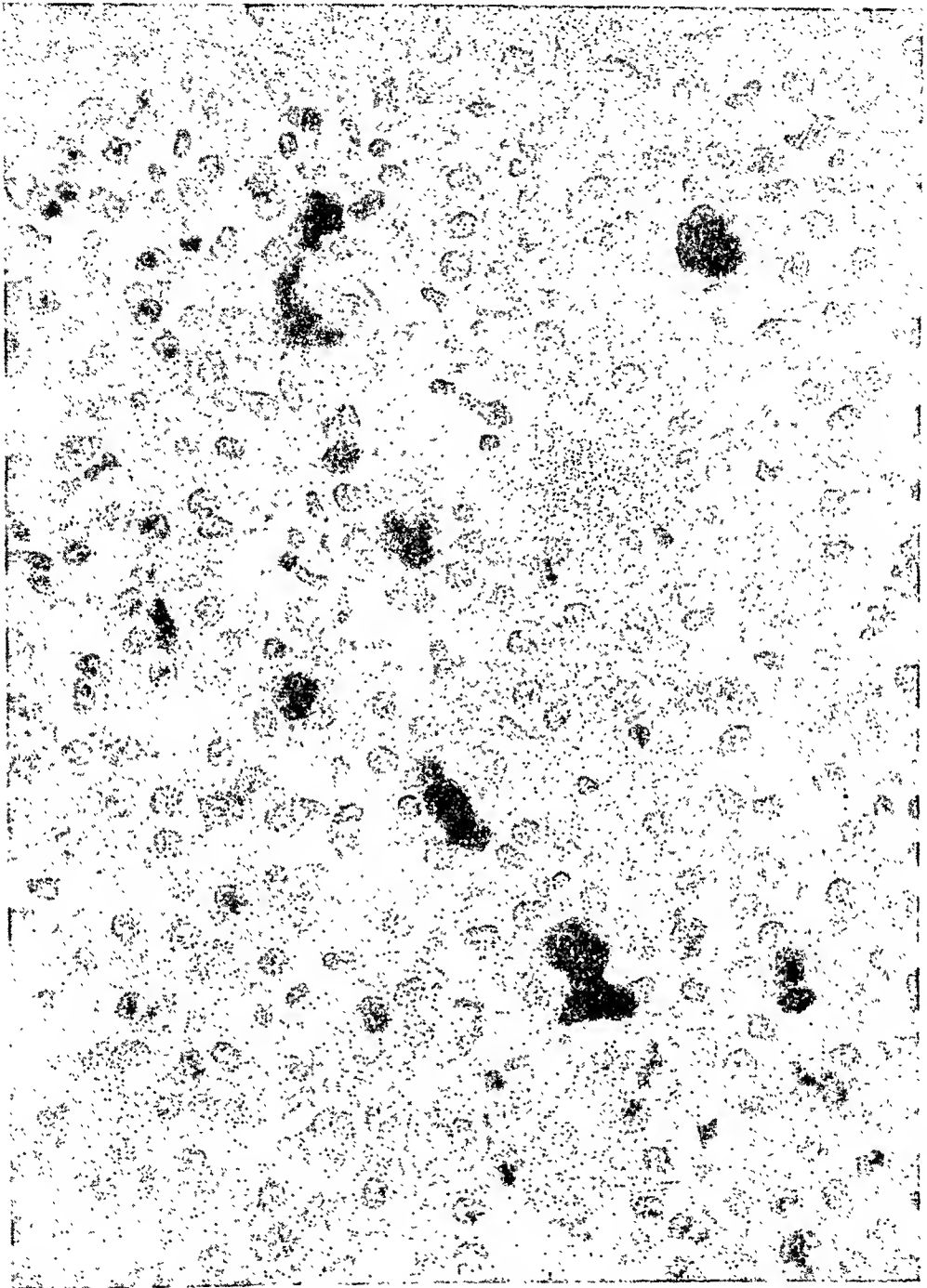


FIG. 17. Liver. This section was selected to show intralobular bile stasis. The bile canaliculi are distended with large deeply stained irregular and sometimes lamellated casts. Bordering liver cells show regressive changes and histiocytic infiltration.

*Clinical Comment:* In addition to the numerous tuberous and plain xanthomas patient 5 exhibited eruptive maculo-pustular lesions. This type of eruptive lesion, formerly described by Thannhauser and Magendantz, is not as these authors believed pathognomonic for xanthomatous biliary cir-

rhosis since one of us has observed meanwhile identical eruptions, which appear and disappear intermittently and itch intensively, in rare cases of chronic infectious hepatitis. In contrast to xanthomatous biliary cirrhosis, skin xanthomas are not known to appear in chronic infectious hepatitis notwithstanding the fact that in these cases cholesterol, but not lecithin, is moderately increased in the serum.

Patient 5 did not show comparatively high cholesterol values. The cholesterols present as esters were already diminished one and one-half years after the onset of the disease; other cases observed maintained a normal proportion of total cholesterol to cholesterol present as esters for a long time. This case deviated from the pattern of cholesterol accumulation observed in other cases of this disorder. The chemical findings alone would not be sufficient to establish the clinical diagnosis beyond doubt if the histological findings of pericholangiolitic biliary cirrhosis in the biopsy at the beginning of the disease did not suggest the diagnosis of xanthomatous biliary cirrhosis.

*Case 6.* A 43 year old farmer's wife was admitted by Dr. W. C. Burrage to the Joseph H. Pratt Diagnostic Hospital on April 16, 1947.

*Present Illness:* In January 1946 the patient visited her physician because of nose bleeds, enlarged abdomen, light-colored fetid stools and much flatus. Her doctor informed her that she was jaundiced and her liver was enlarged. He gave her bile salts and vitamins and also placed her on a high-calorie, high-protein, high-carbohydrate and fat-free diet. One month later she complained of pruritus. She also experienced a pain in the right chest region with a fever of 104° F. Sulfadiazine was prescribed, and the temperature rapidly returned to normal. The patient remained in bed for approximately six weeks and was then referred to a specialist in Halifax. There a chest film was made, an upper gastrointestinal series was done, and her stools and blood examined. Her hemoglobin was normal. Her liver was still enlarged. Everything else was normal. The patient continued a fairly normal existence, getting adequate rest and subsisting on the regimen outlined by her physician. However, she slowly and gradually went off the diet. The pruritus became more intense. The physician increased her bile salts. As no improvement was noted, the patient was referred to Dr. Burrage of Maine, who recognized the nature of her disease and advised her to enter our hospital.

It was noted on admission that the lesions on her body, first noted by the patient's sister on September 1, 1946, had steadily increased in number. Almost every crease of her body showed hard, raised yellow nodules of varying sizes. Nodular xanthomas were seen on the hands, elbows, eyes, and both lower extremities as well as the trunk and back. Eruptive maculo-pustular lesions with a red base and a depressed head were also visible on the extremities. The true yellow xanthomas elsewhere over the body looked different and were not inflamed. The hands had always been dry. The pruritus, continuous since February, was possibly more intense. The bile salts had seemed to darken the stools, which were more brown than yellow. The really light stools observed approximately one month prior to admission, seemed to occur with excessive fat indulgence. The stools were bulky and well formed, and the odor was lessening. She had never noticed black or bloody stools. From the beginning of her illness the urine had been dark—a dark amber color. At times the odor was strong. She seldom had nose bleeds recently nor bleeding from any of the orifices. Occasionally her gums bled after she brushed her teeth. The patient menstruated last, one year before admission at the onset of her present illness. Her jaundice had varied in intensity. At times she had been quite yellow, at other times considerably

clearer of jaundice but she was never completely free of it. The patient had lost her voice two weeks ago. This began with a cold, and throat irritation. She had noticed a change in her voice since the fall of 1946 and could not sing as well as previously.

*Family History:* Mother is living and well at the age of 73. Her father drowned at the age of 30. Three sisters are all well. No family history of cancer, tuberculosis, kidney disease, heart disease, hypertension, nervous disease, convulsions or diabetes. No family history of similar lesions or allergy.

*Past History:* The patient had the usual childhood diseases. She had scarlet fever when she was approximately 20 years of age. No major operations or serious illnesses.

*System Review:* No headaches, vertigo, syncope, blurring, diplopia, scotomas, tinnitus or otorrhea; epistaxis has been mentioned. No dysphagia. No cough or chest pain. The patient stated that she perspired profusely, may have had hot "flashes." No hemoptysis, ankle edema, shortness of breath or palpitations. Appetite enormous; she stated that she could not get enough to eat. Her weight had been stationary. No nausea, vomiting or constipation. Since the onset of her present illness she has had more frequent bowel movements, now numbering two to four a day; in contrast to two bowel movements formerly. She has had nocturia, three or four voidings. Previously there had been nocturia once. There is no burning, dysuria or hematuria.

*Habits:* The patient does not smoke or drink. At the present time she is subsisting on a high-calorie, high-protein, high-carbohydrate, low-fat diet. She takes bile salts, iron and vitamins. She has also been given "biotol," and amino acid preparations.

*Social History:* She was born in New Brunswick, Canada, and came to this country at 18 years of age. She trained as a nurse at the Poughkeepsie Hospital. She married at the age of 37. Her husband is seven years her senior. They have two children. Her husband and children are well.

*Physical Examination:* Temperature 99.4°. Pulse 82. Respirations 18. Height 5' 3". Weight 127½ pounds. Blood pressure is 120/70 in the recumbent position. The patient is a well-developed middle-aged woman in no acute physical distress. She is pleasant, coöperative and intelligent. She speaks in a whisper because she is hoarse. The skin is dark brown and peppered with xanthomas which are elevated, yellow and hard and which vary in size considerably. Xanthomas are present practically all over the body, the neck, chest, back, arms, hands, and lower extremities. There are also maculopapular lesions on the lower extremities which are different from the yellow xanthomas. There is cracking about the creases of the hands, which are hard and dry and practically covered with xanthomas. Hard yellow elevated nodular lesions also appear over the dorsum of the hands and seem to be localized over the joints. Both elbow regions are involved, and lesions are found in the antecubital fossae and over the extensor joint surface. Both axillae exhibit white smooth hard lesions. The back is peppered with lesions, numerous areas of dark pigmentation unassociated with whitish discoloration are present. There is a chamois-like color to the skin around both eyes. The face is symmetrical. No sinus or mastoid tenderness. No exostoses. The auditory acuity is good. The tympanic membranes are intact. The pupils are round and equal, react briskly to light and accommodation. The extraocular movements are normal. There is no nystagmus, blepharitis, conjunctivitis, exophthalmos or enophthalmos. The ophthalmoscopic examination reveals well-defined discs with no retinal abnormalities, no hemorrhages or exudates. Nose: No septal deflection, rhinitis, perforation or polyps. *Oral Cavity:* No cheilosis. The teeth are in good repair. The tongue is not coated; it projects in the midline. The papillae are prominent. No stomatitis, gingivitis, glossitis or pharyngitis. There are no lesions similar to those observed over the body. *Larynx:* The patient has been hoarse for three months. The vocal cords are thickened. No definite xanthoma could be seen on

the infiltrated cords. *Neck*: No rigidity, tracheal deviation, thyroid enlargement or cervical adenopathy. The chest is symmetrical. The breasts are small, free of masses. No erosion of the nipples. There are small insignificant nodes in both axillae. The lungs, except for the right base, are clear to auscultation and percussion. The diaphragmatic excursions are good. The heart is normal in size and position; the rate is normal; the rhythm regular. There is a Grade I to II systolic murmur heard over the entire precordium. The abdomen is distended and asymmetrical. There seems to be a definite fullness in the right side of the abdomen and bulging in the right flank. On palpation one can feel a tremendously enlarged smooth liver that fills the entire abdomen except for the left flank. The spleen can be definitely felt and palpated two fingers below the costal margin. No inguinal hernia or adenopathy. The extremities are symmetrical. The lesions present over both lower extremities have been mentioned. No peripheral edema. The dorsalis pedis pulsations are good. Skeletal system: The spine exhibits the normal curvatures. No tenderness elicited on percussion along the spine. The joints are all freely movable. Neurological examination: The muscle tone and strength good. No atrophy, paralysis, fibrillation or tremor. Coördination tests well performed. Sensations intact. Reflexes: Active and equal bilaterally. No pathological reflexes were elicited. Pelvic examination: External genitalia normal. There is a Grade III to IV cystocele. Marital introitus. The cervix is normal in position. There is a polyp protruding from the cervical os. The uterus and adnexa were not palpated. Rectal examination: Sphincter tone good. No hemorrhoids or masses outlined. The stool was brown. There is no fluid in the abdomen. No shifting dullness.

*Laboratory Data*: Urine: Reaction alkaline; sugar 0; albumin 0; specific gravity, 1.023; on microscopic examination rare red blood cells and leukocytes; few squamous epithelial cell and very rare mucous threads; bile +; urobilinogen ++, urobilin ++++, Wallace and Diamond test, 1:80.

Blood: Hemoglobin 11.5 gm.; red blood cells 3.57 millions; color index 1.02; white blood cells 9,450; polymorphonuclears 69 per cent; band forms 5 per cent; lymphocytes 20 per cent; monocytes 6 per cent. Blood smear: Occasional target cell. Few macrocytes. Rare polychromatophilia. No rouleaux. Platelets normal in number.

Blood chemistry: F.B.S. 87 mg. per cent; total serum proteins 8.0 mg. per cent; albumin 3.7 mg. per cent; globulin 4.3 mg. per cent. Total bilirubin 9.0 mg. per cent; direct 7.1; indirect 1.9.

TABLE VI  
Lipid Findings in Serum of Case 6

	April 14, 1947	April 17, 1947	June 2, 1947	Sept. 1947
Serum: appearance	yellow-green clear	yellow-green clear	yellow-green clear	
Cholesterol—total	920	962	850	616
Cholesterol—free	830	915	750	448
Cholesterol—esters	90 (9.8% of total chol.)	47 (4.9% of total chol.)	100 (11.8% of total chol.)	168 (27% of total chol.)
Phospholipid total	1750	1325	1750	
Saponifiable lipids: (Lecithin and cephalin)		1071	1200	
Total fatty acids	1540	1280	1700	
Neutral fat	235	230	0	
Bilirubin total	9		6.9	
Total protein	8			
Albumin	3.7			
Globulin	4.3			

Serology: Blood sedimentation rate, 20 minutes 28; 1 hour 81. Prothrombin time 26 seconds. Control, 24 seconds.

*Pathology.* The specimens consisted of two small fragments of liver tissue, each approximately 0.4 by 0.3 by 0.2 cm. On each, there was a small but smooth area of capsular surface. The tissue was heavily bile-stained, finely nodular, and firm. It cut with resistance and had a coarse texture.

*Microscopic Examination:* Five sections were studied immediately on this viable, fresh unfrozen and unfixed tissue. Each showed a lengthening and widening of the portal areas with an increase in interstitial fibrous tissue, and a very rich lymphocytic infiltration. The central veins and the lobular pattern for the most part, were well preserved. By elongation and fusion with one another, the enlarged portal areas had already formed a well advanced perilobular form of cirrhosis. No bile was seen in these widened portal areas. This stood out in marked contrast to the extreme degree of bile retention within the lobules. All sections were studied with a polarizing microscope and all failed to reveal any doubly refractile fat. No xanthoma cells were found in any part of the sections. The portal veins and arteries in the portal areas were inconspicuous. The terminal bile ducts were very difficult to find. There was no bile within any of the terminal bile ducts. While the portal areas and lobules were clearly demarcated from one another, it was possible to trace delicate icicle-like projections of fibrous tissue from the portal areas out between the liver cells of the peripheral zones of many of the lobules. A "rapid section diagnosis" made at the moment of biopsy was that of chronic pericholangiolitis with beginning pericholangiolitic biliary cirrhosis. There was no evidence of tumor, or signs of extrahepatic biliary obstruction, and there was no evidence of an active cholangitis. The degree of liver cell degeneration was very limited.

Later, when the paraffin sections were ready, a very careful histological study confirmed the earlier diagnosis. Many of the lobules were well preserved and many of the central veins remained unchanged in the centers of the lobules (figure 18), but in other areas central veins lay in close communication with widened portal areas (figure 19). There was considerable loss of liver cells from the peripheral zones of the lobules. The most striking finding was the presence of an unusually active chronic proliferative inflammatory reaction in the interstitial tissue of the portal areas. There were many polymorphonuclear leukocytes throughout the inflammatory granulation tissue. The junction ducts were increased and numerous. They lay embedded in inflammatory granulation tissue. They branched, twisted and turned, but could be readily followed from the lobules into the granulation tissue of the portal areas. There were very few recognizable terminal bile ducts or cholangioles. In the paraffin sections, bile casts were numerous in bile canaliculi and in dilated junction ducts, but no casts were visible in the terminal bile ducts. The inflammatory infiltration extended well out between the liver cells in the peripheral zones of the lobules and in this area the liver cells showed degeneration and necrosis.

The overall picture was one of a very active chronic interstitial hepatitis centered about the terminal bile ducts and junction ducts at the outer margins of the lobules. There was an increase in fibrous tissue, a widening and fusion of the portal areas, and a well advanced perilobular fibrosis. No xanthoma cells were found in any of the portal areas. The final diagnosis was chronic pericholangiolitic biliary cirrhosis.

This case shows the greatest destruction of liver tissue of any of the early biopsies and in some areas it is possible to find fields that are indistinguishable from those seen in subacute and chronic cases of infectious hepatitis (figures 20, 21, 22). The complete picture, however, was distinctly one of an inflammatory reaction concentrated in the portal areas.



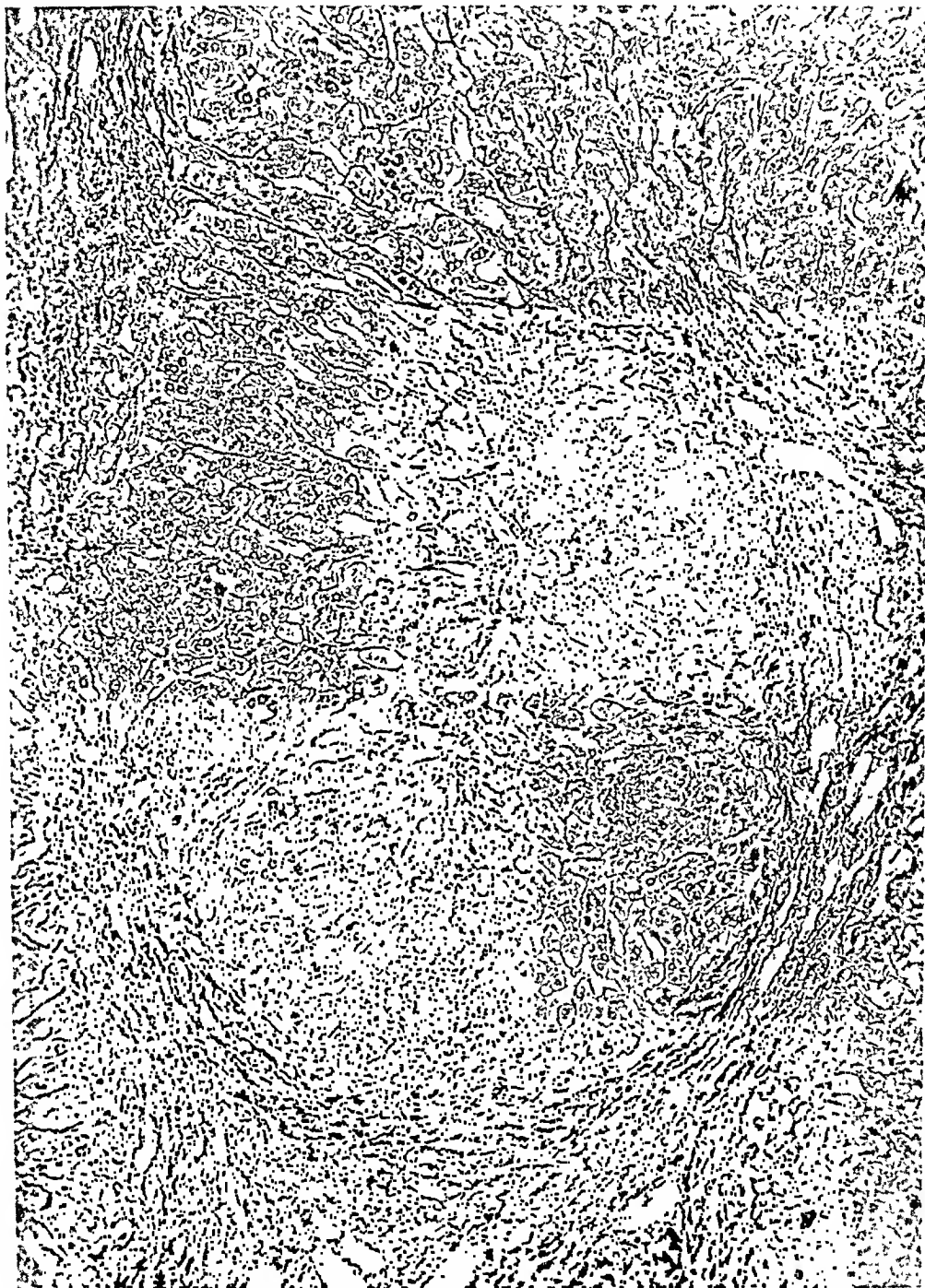


FIG. 18. Liver stained for reticulum. A solitary lobule occupies almost the entire field with the central vein in the middle. There is no increase of reticulum within the lobule although it is slightly concentrated in the central zone. In the peripheral zone there is not only a condensation, but an actual increase radiating out from the portal area.

*Clinical Comment:* This patient (Case 6) exhibited most extensive xanthomatous lesions, especially of the "plain" variety. Conspicuous not only on both eyelids and on the creases of the palm, these "plain" lesions were developed almost every place where the cutis is rather loosely attached to



the subcutaneous tissues and wrinkles in longitudinal folds such as around the neck, in the axilla, and on the folds of the buttocks. The patient also had itchy maculo-pustular eruptions on the trunk and especially on both legs. It should again be emphasized that these maculo-papular lesions are not the result of scratching.

The patient's liver was extremely large and almost filled the whole abdomen while the spleen extended only about one inch below the left costal margin. The liver, visible while a laparotomy for the biopsy was performed, revealed a fine granular surface with longitudinal scarring. Its color was reddish brown. Ascites was not present in the abdominal cavity.

The analysis of the serum lipids showed high values for lecithin (1071 mg. per cent) and total cholesterol (962 mg. per cent) but only 5 per cent of the total cholesterol was present as esters. These findings may be interpreted as indicative of severe damage of liver parenchyma. In this case, in contrast to other instances of acute damage of liver parenchyma, such as in acute yellow atrophy of the liver or in fulminant cases of acute infectious hepatitis, the drop in cholesterol esters (Estersturz<sup>28</sup>) did not occur together with low total cholesterol but on the contrary with very high cholesterol in the serum. This remarkable phenomenon may signify that increased cholesterol formation is not checked in xanthomatous biliary cirrhosis even when an intercurrent parenchymatous damage impairs the esterification of cholesterol. It is unlikely that retention alone causes this phenomenon of very high cholesterol and very low esters. The increased formation of cholesterol is, however, lessened when in the course of the disease the liver parenchyma is replaced by fibrotic tissue as seen in Case 1 and Case 2.

### GENERAL DISCUSSION

*Age and Sex:* The patients in the group of reported cases of xanthomatous biliary cirrhosis, have been between 30 and 50 years of age, with the exception of a seven year old girl described by Freda K. Herbert.<sup>17</sup> With the exception of Moxon's case,<sup>2</sup> the cases reported so far<sup>16, 17, 18, 19, 20, 22</sup> have been female patients.

In regard to reported male patients with hepatosplenomegaly, slight jaundice, melanotic pigmentation of the skin, increased total cholesterol and lecithin, and skin xanthoma, the question arises as to whether these cases should be classified under xanthomatous biliary cirrhosis. Cantarow and Bucher,<sup>29</sup> in a paper titled "Hemochromatosis," described a 45 year old man with a large liver and spleen and xanthoma on both eyelids, flexor and extensor surfaces of the elbows and on the creases of both palms. There were also a blue bronze pigmentation and slight jaundice but no glycosuria. (Serum cholesterol: total cholesterol 275 to 490 mg. per cent; cholesterol present as esters 114 to 333 mg. per cent; free cholesterol 33 to 157 mg. per cent.) The autopsy of the patient revealed hemochromatosis of the liver, most extensively in the pancreas and lymph nodes.

Eusterman and Montgomery<sup>18</sup> refer in Chart 1 Case 2 in their paper to a 42 year old male with large liver and spleen, xanthoma of the eyelids, slight jaundice, melanosis and glycosuria. (Serum lipids: total cholesterol 536 mg. per cent; lecithin 557 mg. per cent, total fatty acids 884 mg. per cent.)

One of us (Thannhauser) saw in consultation a 40 year old man with xanthomas on eyelids, elbows, buttocks and creases of the palms. His liver and spleen were considerably enlarged; he was slightly jaundiced and showed deep bronze pigmentation over the whole body but no glycosuria. (Serum lipids: total cholesterol 417 mg. per cent; cholesterol-ester 40 per cent of total cholesterol; total phospholipids 643 mg. per cent; lecithin 600 mg. per cent.)

It seems unlikely that these three male patients had xanthomatous biliary cirrhosis. The autopsy of the patient of Cantarow and Bucher revealed hemochromatosis of the liver, lymph glands and extensive hemosiderosis of the pancreas resulting in chronic pancreatitis. It seems probable that the two other deeply melanotic pigmented male patients also had hemochromatosis.

Why patients with hemochromatosis develop in rare instances skin xanthoma is a question that cannot be definitely answered. The following suggestions may be offered: 1. In the case of Cantarow and Bucher chronic hemosiderosis of the pancreas may have resulted in hyperlipemia and hypercholesteremia and secondary skin xanthoma. An increase of neutral fat in the serum would have to be expected, if hyperlipemia secondary to chronic pancreatitis was the cause of xanthoma formation in these cases. Unfortunately neutral fat had not been estimated in any of the three cases. 2. The hemosiderin deposits in the liver may have injured and obliterated the same areas of the finest bile capillaries as those which we have described as concerned with the underlying pathology of xanthomatous biliary cirrhosis. This second suggestion seems unlikely since neither the jaundice nor the hypercholesteremia nor the hyperlecithemia were as pronounced as in xanthomatous biliary cirrhosis. In the future a detailed analysis of the serum lipids, especially the presence or absence of hyperlipemia (increase of neutral fat) will clarify the etiology of skin xanthomas in such cases of hemochromatosis.

Concerning the sex incidence of xanthomatous biliary cirrhosis it has to be assumed from present evidence that this syndrome with its typical features has so far been observed only in females.

*Hereditry:* In none of the cases reported was a familial occurrence revealed by the history. The group of "hypercholesteremic familial xanthomatosis," characterized by tuberous and plain xanthomas of the skin, tendon xanthoma and atheroma formation on the inner lining of the arteries, is a disorder which runs in families.<sup>14, 15, 20, 31, 32</sup> Thannhauser and Magendantz<sup>14, 15</sup> formerly believed that xanthomatous biliary cirrhosis also belonged to this group.

This opinion can no longer be maintained since in the meantime no familial incidence of xanthomatous biliary cirrhosis has been found in the cases described. It now is apparent that xanthomatous biliary cirrhosis is primarily a liver disease and a clinical entity by itself.

*Clinical Features:* The onset is insidious. The patients complain of itching of the skin, which is speedily followed by jaundice of the obstructive type, i.e. bilirubin giving the direct and indirect van den Bergh reaction is found in the serum. The jaundice remains until the fatal end of the disease. The grade of the jaundice does not vary much during the course of the disease and seems rather independent of the development of the skin xanthomas and of the fluctuation of the cholesterol and lecithin values in the serum. Fever or chills are not a feature of the disease. The development of fever is a sign of an intercurrent complication (see Case 1). The absence of fever probably explains in part why the patients feel relatively well during the course of the disease and are able to do their housework. The skin xanthomas may appear simultaneously with the jaundice or in most cases develop many months later. The tuberous deep yellow xanthomas are observed on the face, the elbows, the arms, fingers, buttocks and the distal parts of the lower extremities. Plain xanthomas appear on the eyelids, the creases of the hand and in rare instances also in places where the skin is loosely attached to the underlying tissue forming folds as in the axillary folds and in the folds of the skin of the buttocks. The localization of the skin xanthoma is different from that in the so-called "disseminata" type of xanthoma characteristic of "normocholesteremic xanthomatosis," as seen in Schüller-Christian's disease (lipid granulomatosis, eosinophilic xanthomatous granuloma). In this latter entirely different type of disease the xanthomas are light yellow or deep sepia brown, disseminated around the neck and the trunk and arranged in linear clusters in the axilla. The skin xanthomas in xanthomatous biliary cirrhosis persist during the entire course of the disease. The liver and spleen also remained enlarged. In some cases (Case 6) the liver extends in the midline over the umbilicus; in others it is only moderately enlarged. The surface of the liver is very firm but not nodular. The color, visible in early exploration is brownish-red or green, and the surface is smooth or slightly granular. Later stages reveal longitudinal scarring and larger granulation of the surface. Ascites is not a feature of the disease. Sometimes a peculiar maculo-pustular eruption, which appears and disappears intermittently, is seen all over the body, and especially on the trunk and the legs. First inspection gives the impression that these lesions are only the result of scratching but upon closer observation one sees the sunken-in head of the lesion mostly covered by a small crust. The eruption is inflammatory in nature and does not contain foam cells. Since similar eruptions occur in rare cases of chronic infectious hepatitis with chronic jaundice and moderately elevated cholesterol in the serum, this type of maculo-pustular eruption, even if most frequently observed in xanthomatous biliary cirrhosis, is not an exclusive feature of this disease.

Analysis of the serum lipids provides the most decisive findings for the diagnosis of xanthomatous biliary cirrhosis. The serum is transparent and not creamy throughout the disease. It contains normal or very low amounts of neutral fat despite its enormously increased content of cholesterol and lecithin. At the beginning the total cholesterol values of the serum may surpass 1500 mg. per cent. The cholesterol present as esters in the first year is normal, i.e. 70 to 75 per cent of the total cholesterol. The percentage of the esters may even be higher than these normal figures. After several years, the values for total cholesterol decrease but remain high; the percentage of the cholesterol present as esters becomes lower, and the free cholesterol is more prominent. The high values for lecithin decrease slowly with those for total cholesterol but are found even in the last stages. A tendency towards bleeding, such as is observed in other forms of chronic jaundice, is not marked. The prothrombin time, in the first years, is usually normal. In the final phase, however, bleeding from the gums, and vomiting of blood due to rupture of esophageal varices is observed. Profuse hemorrhage from esophageal varices is the most common terminal event. The development of portal congestion occurs, however, very late in the course of the disease. Roentgen-ray pictures of the esophagus during the development and the height of the disease do not show esophageal varices. At this stage other signs of portal congestion like ascites or spider veins are absent. Hepatic insufficiency resulting in hepatic coma was not observed in our cases. Liver function tests are not of great value for the diagnosis of xanthomatous biliary cirrhosis since the clinical symptomatology is typical in all cases, namely: (1) Skin xanthoma of the plain and tuberous variety. (2) Enlarged liver and spleen. (3) Obstructive type of jaundice of years' duration. (4) Extremely high values for total cholesterol as well as for lecithin. (5) The serum is transparent and not milky because of its normal or rather low content of neutral fat.

### PATHOLOGY

*Early Biopsies:* In the portal areas there was a chronic proliferative and exudative inflammatory reaction, which was most concentrated about the junction ducts (canals of Hering) and terminal bile ducts (interlobular bile ducts or cholangioles) at the periphery of the lobules (figures 1, 2, 14, 15). The portal areas were larger, broader and longer than usual and often fused with one another to form rings of perilobular fibrosis (figure 18). Inflammatory granulation tissue extended into the periphery of the lobules. It blocked canaliculi, destroyed liver cells and collapsed many sinuses (figure 3).

The larger bile ducts were patent and empty. The small interlobular bile ducts were very difficult to find and in many of the portal areas there were none. The junction ducts which in a normal liver are so inconspicuous, were numerous, elongated, branching and tortuous. Some were dilated and filled with bile, others were collapsed and empty. None of the ducts con-

tained leukocytes, although several types of inflammatory cells including lymphocytes, plasma cells, histiocytes, neutrophils and occasionally eosinophils, richly infiltrated the surrounding granulation tissue.

The lobular pattern of the liver was well preserved and most central veins bore a normal relationship to the surrounding liver parenchyma. Large and

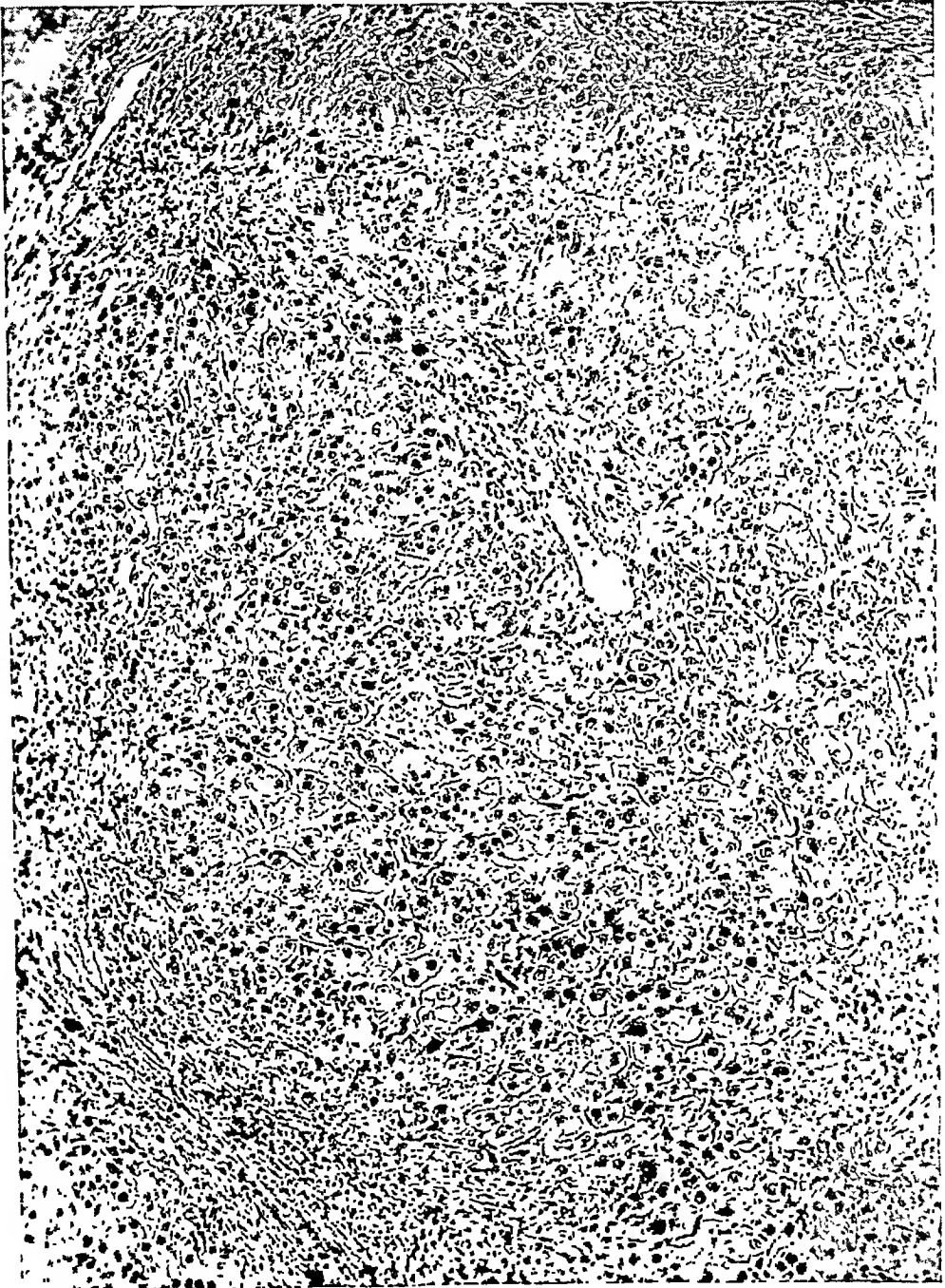


FIG. 19. Liver, showing an intact lobule with central vein clearly visible. The trabecular pattern is somewhat distorted and compressed and many small liver cells are mixed with those of normal size. A zone of inflammatory granulation tissue encircles the periphery of the lobule.

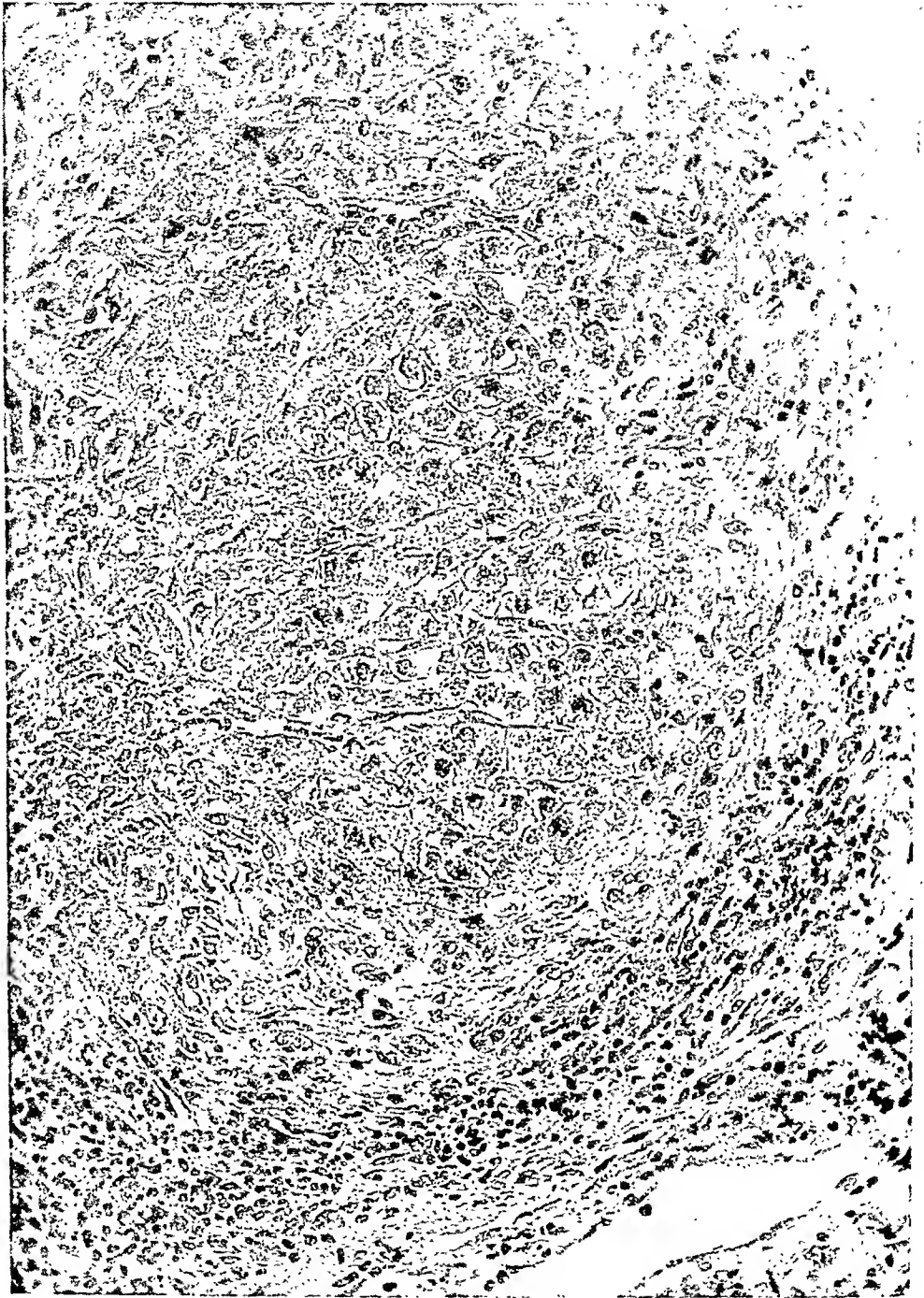


FIG. 20. Liver. A small nodule of compressed liver cells and sinuses. There is no central vein. This nodule of liver tissue is completely encircled by a widening zone of inflammatory granulation tissue radiating out from the peripheral zones of the lobules.

sometimes lamellated bile casts were fairly numerous within the lobules (figure 17). These distended the canaliculi and often damaged the bordering liver cells. For the most part the liver cells were healthy, few contained fat droplets and some lying in the field of inflammatory reaction about the portal areas showed degeneration and necrosis. There were few mitoses and the



presence of closely packed clusters of small cells near the periphery of the lobules suggested a moderate degree of liver cell regeneration (figures 4 and 19).

In one of the four biopsies the damage to the parenchyma was greater than in the others. In this biopsy, in contrast to the other, there were fields

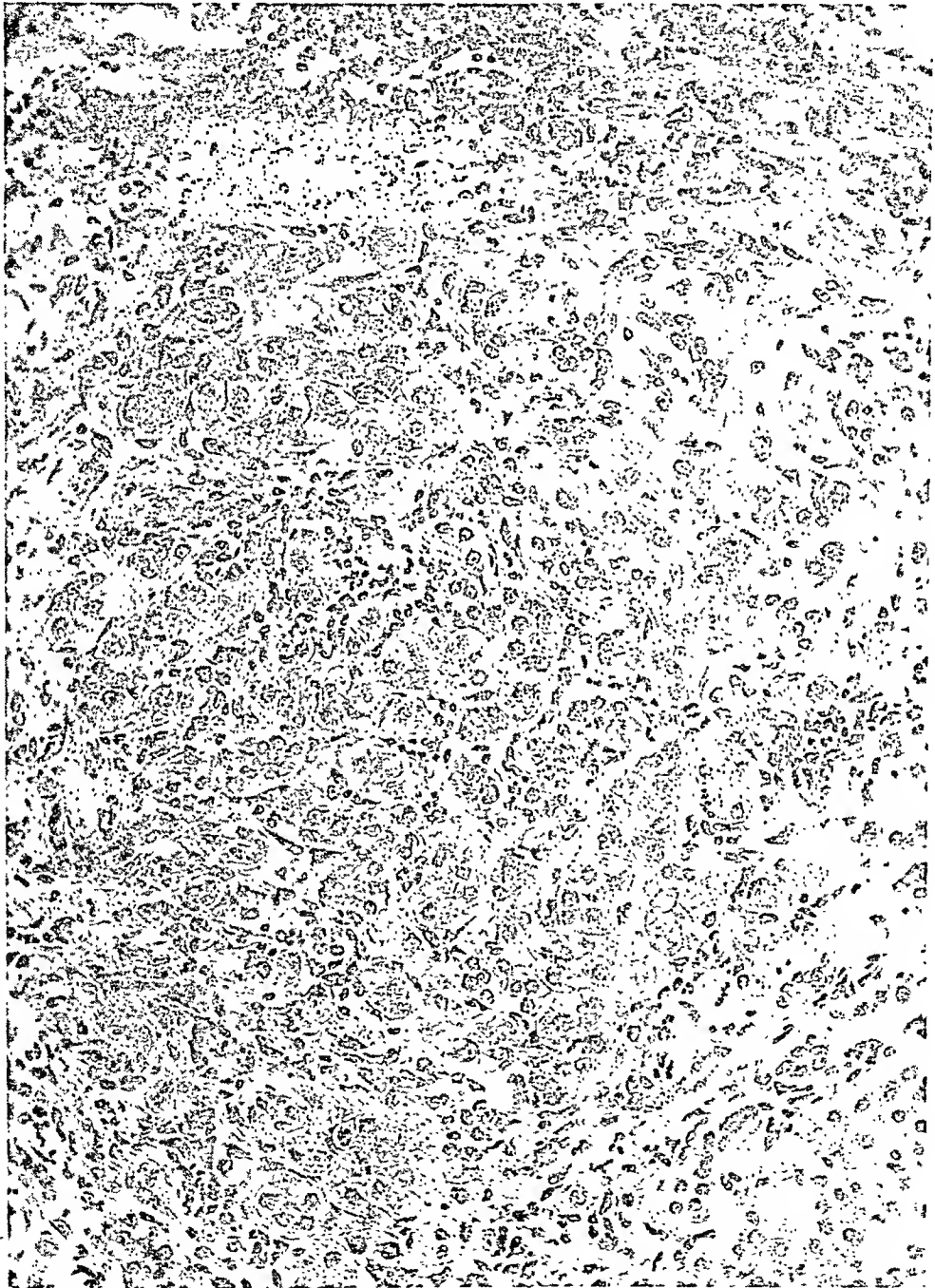


FIG. 21. Liver. This field was selected to show all that remains of a lobule of liver cells. There is an active inflammatory reaction at the periphery and extending along the sinuses between the liver cells. This was an unusual finding, but its resemblance to pictures seen in infectious hepatitis is at once obvious.

in which the inflammatory reaction had cut deeply into the centers of the lobules (figure 6). In this way central veins became linked with portal areas, and large and small islands of liver cells became isolated from the body of the parent lobules (figure 20). These islands, in turn, seemed to melt away to become replaced by inflammatory granulation tissue (figure 22). In one area an entire lobule had been destroyed and was now substituted by fibrous tissue.

The one fundamental histological finding common to all four biopsies was a chronic inflammatory reaction in the interstitial portal areas. It began as chronic pericholangiolitis and spread over into the peripheral zones of the adjacent lobules.

*Autopsy Findings:* To understand the development of the different types of cirrhosis it is necessary to know these types in all their stages. A study of this material afforded the opportunity to compare adequate sections from the livers of patients during life with sections obtained months and years later.

Grossly, the livers of the two patients who came to autopsy were large, firm, and cobbled. They weighed 2600 and 2800 grams respectively. On section the texture was coarse and bile-stained. There were no depositions of cholesterol in the mucosa of the gall-bladder or in any of the bile ducts. There were no concretions and finally, there was no suggestion of any type of extra-hepatic biliary obstruction.

The histology was much more complex and confusing than in the earlier biopsies. In a few areas the central veins, central zones and mid-zones were still recognizable, but for the most part, the normal lobular pattern in these late cases was severely distorted. Bands of fibrous tissue divided the parenchyma and not infrequently replaced whole lobules.

The parenchyma was composed of irregular cords of liver cells separated by edema fluid, dilated sinuses and fibrous tissue (figures 7 and 8). Here and there, the Kupffer cells were large, swollen and filled with lipoid, and nests of these occasionally distended the sinuses and compressed the adjacent trabeculae. There was much bile stasis with bile in the canaliculi, liver cells and sinuses.

The larger bile ducts were collapsed and empty. The terminal ducts were inconspicuous and embedded in fibrous tissue. In none of the ducts was there either an inflammatory exudate or any evidence of xanthomatosis.

The large size of the liver, the extensive fibrosis, the fragmentation of some lobules and the total loss of others, the nodules of regenerated liver tissue, the compression and interruption of liver cords by fibrous tissue, the patchy bile stasis, the intralobular lipoid deposition and finally, the presence of a still active chronic inflammatory reaction in portions of the interstitial tissue, all combined at this late stage to form a very confusing histological picture. If such a damaged liver were to be seen for the first time without an earlier biopsy, its pathogenesis would be difficult to unravel and its classi-



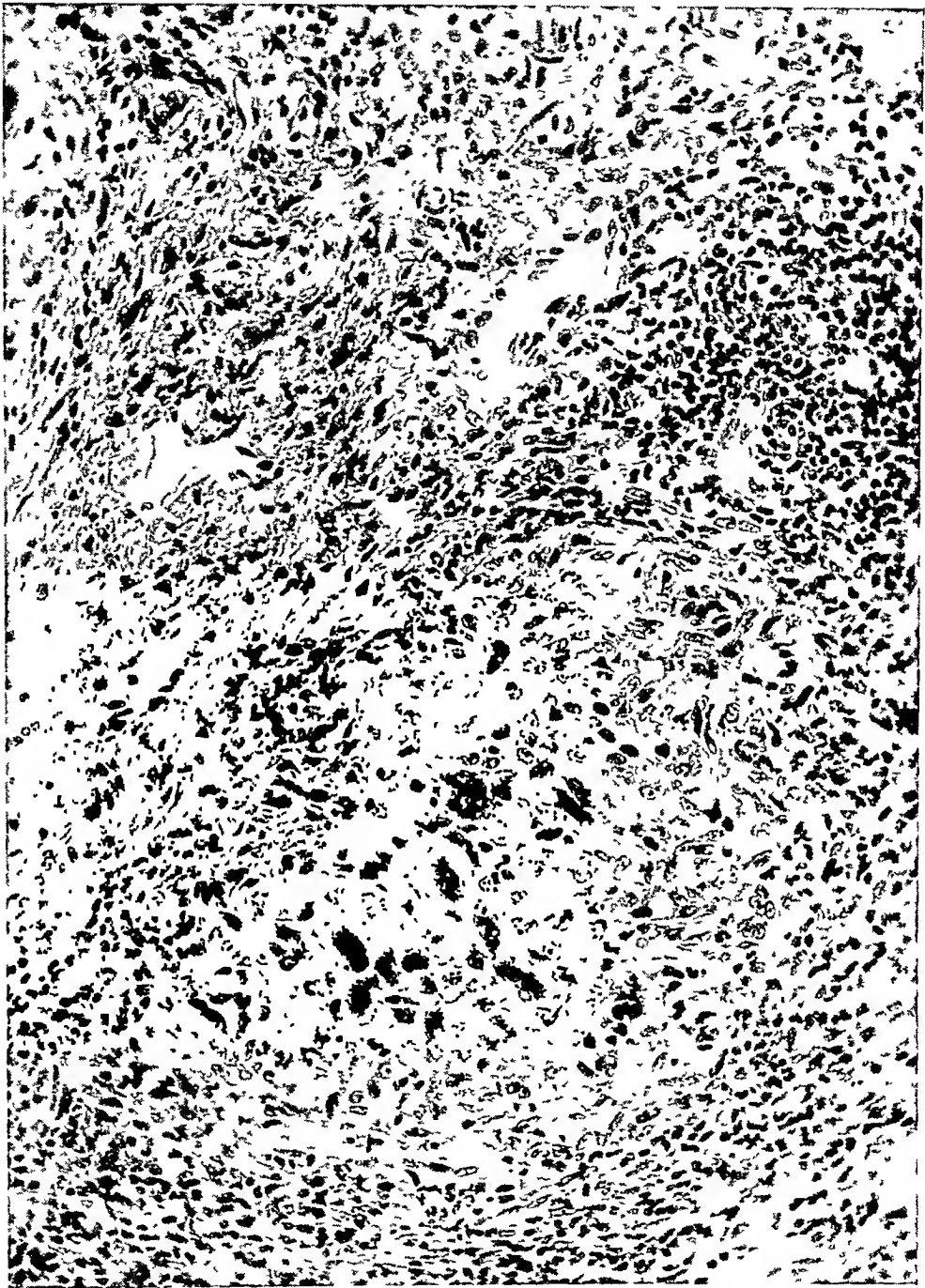


FIG. 22. Liver. This field was selected, and it is the only one of its kind in the entire section, to show how completely a lobule may be destroyed in this expanding zone of inflammatory granulation tissue. In the center of the field there are few moderately well preserved liver cells compressed together by this margin of granulation tissue. This particular field shows, perhaps, the most striking lesion in the biopsy, yet it is only fair to say that it was found only after long search and is not representative of the rest of the biopsy. All transition between this lesion and the inflammatory reaction in the portal areas could be identified.

fication would be uncertain. In this late stage it could easily be misinterpreted as an advanced stage of Laennec's cirrhosis.

Moxon<sup>2</sup> and Fagge<sup>23</sup> in 1873 reported the autopsy findings of two cases showing xanthoma of the skin with either atheromatous changes on the inner linings of the arteries or xanthoma formation on the linings of the bile ducts. Pye-Smith<sup>3</sup> in the same year described a third case of cutaneous xanthomatosis in which the patient showed cholelithiasis and dilatation of the extrahepatic biliary ducts. The liver of this patient showed changes suggesting a slight degree of interstitial fibrosis. Of this particular case Pye-Smith wrote: "The patches in the ducts looked just like atheroma in the artery with which condition, indeed, they corresponded histologically."

On this evidence, Thannhauser and Magendantz suggested that xanthoma formation of the bile ducts resulting in xanthomatous scar tissue might be the cause of the clinical syndrome which they had designated as xanthomatous biliary cirrhosis. It was their opinion that the development of the xanthoma of the skin as well as the xanthoma formation within the bile ducts, was the expression of a primary systemic disease characterized by an increased formation of cholesterol with hypercholesteremia (hypercholesteremic xanthomatosis). The xanthomatous involvement of the large bile ducts and their partial obstruction was thought to be the primary event which resulted later in this special type of biliary cirrhosis (xanthomatous biliary cirrhosis).

This opinion can no longer be maintained since our biopsies taken during the early stages as well as the autopsies years later of cases of xanthomatous biliary cirrhosis did not reveal the anticipated xanthomatous changes in the linings of the bile ducts. The biopsies in the early stages showed a proliferative and exudative inflammatory reaction about the smallest of the interlobular cholangioles and junction ducts extending into the periphery of the lobules. The autopsies showed cobbling of the liver, marked enlargement of the liver and advanced cirrhosis. At this late stage the initial and characteristic pericholangiolitic changes were difficult to see. When such a cirrhotic liver is seen without previous biopsy, an accurate diagnosis would be difficult and its pathogenesis would be uncertain. It is now believed on the basis of biopsies and autopsies of cases showing the clinical syndrome of xanthomatous biliary cirrhosis in the absence of any obstruction of the large ducts, that the histopathological findings in the liver justify the recognition of a special type of cirrhosis which may be designated anatomically as "pericholangiolitic biliary cirrhosis."<sup>51</sup>

*Etiology:* On the basis of the autopsy findings of Addison and Gull,<sup>1</sup> 1851, as well as Moxon,<sup>2</sup> 1873, and Pye-Smith,<sup>3</sup> 1873, Thannhauser and Magendantz<sup>14</sup> suggested that xanthoma formation of the larger bile ducts resulting in scar tissue may be the cause of the clinical syndrome described as xanthomatous biliary cirrhosis. These authors also believed at this time that xanthomatous biliary cirrhosis is a part of the syndrome of hypercholes-

teremic familial xanthomatosis, which is characterized by (1) tuberous and plain xanthoma of the skin, (2) tendon xanthoma and (3) atheroma formation of the inner lining of the blood vessels and (4) heredity. This etiologic conception of the disease must be abandoned since neither surgical exploration, early biopsies of the liver nor autopsied cases reported in this paper revealed xanthomatous changes of the larger bile ducts which may have resulted in this type of biliary cirrhosis. Xanthoma formation of the lining of the bile ducts, as observed by the early authors, may occasionally occur as a rare side of xanthoma formation, but it is not the cause of this special type of biliary cirrhosis since it was not found by surgical exploration (Case 1) or at autopsy in the discussed cases.

One of us (MacMahon) found in the early biopsies a non-specific chronic inflammatory reaction centered around the smallest bile ducts and junction ducts in the portal areas, which is characteristic of the disease under discussion. There was blocking of the finest bile ducts and subsequent intra-lobular bile stasis. The larger bile ducts were patent and free. Thannhauser<sup>24</sup> has suggested an imbalance of cholesterol formation and excretion as the cause of xanthomatous biliary cirrhosis. At the outset of the disease the accumulation of cholesterol and lecithin in the serum might be caused by an increased formation of these substances in the liver as a result of a functional disturbance of the liver cells. Since liver biopsies have already revealed in the early stages of the disease anatomical changes around the finest bile capillaries, it seems doubtful whether an increased formation of cholesterol and lecithins ought to be assumed in addition to the histologically verified changes of the finest bile ducts, producing bile retention. In other words the question arises whether the extremely high content of the serum cholesterol and lecithin is due only to retention resulting from an impaired elimination or whether both processes, namely increased formation and retention of cholesterol and lecithin are responsible for the phenomenon resulting in the clinical syndrome of xanthomatous biliary cirrhosis. In the comment on the findings of Case 1, page 135, this problem is extensively discussed; therefore, only the main points are repeated. (1) The high cholesterol and lecithin levels of the serum are only moderately reduced after the beginning of diet treatment where the exogenous quota of animal cholesterol was almost completely restricted. This observation suggests that an excessive endogenous production of cholesterol and lecithin persisted during this period of restriction almost free of animal cholesterol intake. (2) The cholesterol concentration in the serum of Case 1 decreased markedly and was almost normal in the final period of the disease because an intercurrent tuberculous disease with miliary dissemination of tuberculous tissue in the liver caused the replacement of the liver parenchyma to a large extent. The obliteration of the finest bile capillaries producing the retention continued unchanged during the terminal phase, but not enough functioning liver tissue remained to maintain the formerly increased cholesterol formation.

(3) Complete obstruction of the common bile duct, as effected by occlusion by stone, carcinoma or fibrosis after a surgical accident usually does not result in an excessively high serum cholesterol and lecithin values (1550 mg. per cent and 2120 mg. per cent respectively) as in xanthomatous biliary cirrhosis (Cases 1, 2, 3, 4, 6). During the first stages of xanthomatous biliary cirrhosis at a time when such extremely high values in the serum were obtained as in Case 1, the liver biopsy showed obliteration of the small bile ducts only in some areas of the liver tissue. It therefore seems unlikely that the fibrotic obliteration of the cholangioles found in these areas at the beginning of the disease should result in a much greater cholesterol and lecithin retention than is true of complete obstruction of the common bile duct.<sup>25</sup> In complete obstruction of the common bile duct by stone, carcinoma or surgical obliteration, jaundice of severe grade, considerable increase of cholesterol and a slight increase of lecithin are observed, but skin xanthomas do rarely appear. The few instances of skin xanthoma after surgical obstruction of long duration<sup>18</sup> seem exceptional. In these rare cases the skin xanthomas disappeared with the restoration of the bile flow while in xanthomatous biliary cirrhosis they persist despite the fact that bile is constantly excreted in the intestines.

These considerations favor the suggestion of Thannhauser<sup>24</sup> that the marked accumulation of cholesterol and lecithin at the beginning of xanthomatous biliary cirrhosis is probably not only the result of a retention of bile but also the consequence of an imbalance of increased cholesterol and lecithin production and an inadequate excretion of these substances. The explanation of the finding of excessively high cholesterol and lecithin as the result of hyperproduction of cholesterol and lecithin in xanthomatous biliary cirrhosis remains a hypothesis. Such a hypothesis is, however, supported by the laboratory findings and by a comparison of this and other cases of xanthomatous biliary cirrhosis with other clinical syndromes where the obstruction and bile retention are complete and the only etiological factor. In the cases of complete obstruction the lecithin and cholesterol content of the serum is by far not as high as in xanthomatous biliary cirrhosis despite the fact that in xanthomatous biliary cirrhosis the bile passages are always patent.

*Differential Diagnosis:* The diagnosis of xanthomatous biliary cirrhosis should be ventured only if all five features of this disease are evident.

In the common varieties of biliary cirrhosis<sup>48, 49, 50</sup> neither skin xanthoma nor excessively high cholesterol and lecithin values of the serum are found. In infectious biliary cirrhosis, mostly due to an ascending infection of the biliary tract, periods of elevated temperature interchange with those of normal temperature; the temperature is normal in xanthomatous biliary cirrhosis. Differential diagnosis from acute and chronic infectious hepatitis is based on the absence in these conditions of widespread xanthomatous lesions of the skin and the abnormal lipid analysis of the serum. Xanthomas of the skin appear in xanthomatous biliary cirrhosis early in the disease together with excessively high total cholesterol and lecithin values in the serum. The per-

centage of cholesterol present as esters is high in the first years of xanthomatous biliary cirrhosis, 70 to 80 per cent. In the acute stage of severe hepatitis, however, the total cholesterol in the serum is never much elevated. The percentage of cholesterol present as esters is diminished in severe cases. The lecithin values in the serum do not rise markedly. The hepatosplenomegaly becomes more evident in the chronic stage of infectious hepatitis, but the serum analysis for lipids does not show a substantial increase of cholesterol. In most of the cases of chronic hepatitis the total cholesterol has a tendency to decrease, and the proportion present as esters remains or becomes low. The incidence of skin xanthomas in acute and chronic hepatitis is not mentioned, although the disease occurred in epidemics during the war. Only in one case observed by Watson and Hoffbauer<sup>33</sup> (case 7) did a male patient show xanthelasma of the eyelid. It was not stated, however, whether the isolated xanthoma had already been present before the hepatitis developed.

An eruptive type of xanthomas distributed over all parts of the body may occur together with hepatosplenomegaly as a consequence of various types of hyperlipemia. The hyperlipemia, i.e., the outstanding increase of neutral fat (10 to 60 times of normal) in these cases causes a milky or creamy non-transparent serum, readily recognized with the naked eye. Jaundice, despite the presence of hepatosplenomegaly in the hyperlipemic syndromes, is not observed. The following syndromes belong in this group of primary hyperlipemia with secondary skin xanthomas: (1) Idiopathic hereditary hyperlipemia<sup>34, 35, 36, 37</sup>; (2) Idiopathic non-hereditary hyperlipemia with and without slight glycosuria.<sup>40</sup> This group includes cases of primary hyperlipemia occurring together with hepatosplenomegaly as described by Buerger and Grütz.<sup>38</sup> (3) Secondary (transport) hyperlipemia as observed in severe untreated diabetes or in chronic pancreatitis<sup>39, 40, 41</sup> or in glycogen storage disease.<sup>42, 43, 44</sup> In all these syndromes of primary or secondary hyperlipemia with and without hepatosplenomegaly, the "creamy" hyperlipemic serum and the absence of jaundice immediately exclude a diagnosis of xanthomatous biliary cirrhosis.

Increase of skin xanthoma, chronic jaundice of slight grade, hepatosplenomegaly and considerable increase of cholesterol and moderate increase of lecithin have been described in the aforementioned rare cases of hemochromatosis. It must be admitted that the differential diagnosis of these cases from xanthomatous biliary cirrhosis may cause some difficulty since patients with xanthomatous biliary cirrhosis may also exhibit deep brown pigmentation. Hemochromatosis, however, occurs mainly in males while xanthomatous biliary cirrhosis has so far been reported with one exception only in females.<sup>2</sup> In xanthomatous biliary cirrhosis the extremely high cholesterol and lecithin values are observed at the very beginning of the disease while in these rare cases of hemochromatosis with skin xanthoma, the elevation of the serum lipids and the xanthoma formation occur in the last stages.

The liver and spleen in the generalized form of eosinophilic xanthomatous granuloma (Schüller-Christian's syndrome, normocholesteremic xanthomatosis, lipid granuloma, eosinophilic granuloma) may also be enlarged. In these cases jaundice is never present. The involvement of liver and spleen in this group of "normocholesteremic" xanthomatosis (lipid granulomatosis, eosinophilic xanthomatous granuloma) is part of a systemic granulomatous disorder, which may also comprise skin, lymph glands, lung, bones, dura, and liver. In xanthomatous biliary cirrhosis, however, the liver is the primary seat of the disease resulting in jaundice, hepatosplenomegaly, outstanding accumulation of cholesterol and lecithin in the serum. Xanthoma formation of the skin as well as xanthoma formation of the inner lining of the arteries and in rare cases also of the inner lining of the large bile ducts are secondary to the liver disorder. Neither single foam cells nor nests of foam cells, however, are found in the liver tissue itself in xanthomatous biliary cirrhosis.

*Therapy:* The patient should become a vegetarian since humans do not usually absorb vegetable sterols. All kinds of vegetables, fruits, nuts, salads, cereals and other carbohydrates are allowed. Animal protein should be given only in the form of skimmed milk, egg white (no yolk), or cottage cheese. All animal fats and meat should be eliminated from the diet. Vegetable fats like olive oil, peanut butter, pure vegetable margarine can be used for cooking. A detailed diet has been outlined by Thannhauser.<sup>45</sup>

In addition intramuscular injections of preparations containing all vitamins in ample amounts should be given twice weekly.

This type of diet treatment excludes only the exogenous quota of animal cholesterol but the endogenous production of cholesterol is not influenced and continues. For this reason the therapeutic value of such a diet is limited. The general nutritional condition during the course of the disease, together with the loss of appetite, may impel the physician to deviate from a strict low cholesterol diet. In such instances small portions of lean meat and lean fish may be added twice weekly.

The administration of choline and methionine and other lipotropic substances is not of great value in this disease since neither increased fat transport (low neutral fat in serum) nor a fatty liver is observed in this disease.

## SUMMARY

1. Xanthomatous biliary cirrhosis (pericholangiolitic biliary cirrhosis), with plain and tuberous skin xanthomas, was observed in five cases. The clinical features, the clinical course and the pathology of the disease as visualized in early biopsies and autopsies are described.

2. The clinical syndrome consists of: (a) Skin xanthomas of the "plain and tuberous" variety; (b) enlarged liver and spleen; (c) obstructive type of jaundice of years' duration; (d) extremely high values for total cholesterol (four to eight times those of normal) as well as for lecithin (four to

10 times those of normal in the serum; (*e*) low values of neutral fat in the serum. The serum is transparent and not creamy.

3. The anatomical findings in the early biopsies at the time when the extremely high cholesterol and lecithin values are present in the serum are as follows: (*a*) non-specific, chronic inflammatory reaction centered about the smallest bile ducts and junction ducts in the portal areas; (*b*) blocking of the finest bile ducts and subsequent intralobular bile stasis; (*c*) lack of involvement of large bile ducts; (*d*) absence of foam cells in the liver tissue. The anatomical designation "Pericholangiolitic biliary cirrhosis with plain and tuberos skin xanthoma" is proposed for this clinical syndrome under discussion.

4. The etiology of the disease is discussed. Two possibilities for the etiology are debated: (*a*) The excessively high content of the serum cholesterol and lecithins may be caused only by retention resulting from obstruction of the finest bile capillaries and junction ducts; (*b*) increased new formation of cholesterol and lecithin by the liver together with impaired excretion resulting from the obliteration of the finest bile ducts and junction ducts may be responsible for the clinical features of the syndrome. Various laboratory findings and clinical features of the described cases are in favor of the second explanation of the disease.

5. The disease so far is observed mainly in females. There is no familial occurrence of the disease. It should, therefore, not be classified as formerly suggested<sup>14, 15</sup> under the group of essential xanthomatosis of the hypercholesteremic type (hypercholesteremic familial xanthomatosis). Xanthomatous biliary cirrhosis (pericholangiolitic biliary cirrhosis) is a liver disorder and a disease entity by itself.

6. The differential diagnosis of the disease has been discussed.

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# CASE REPORTS

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## Q FEVER: REPORT OF A CASE IN PENNSYLVANIA \*

By O. HENRY JANTON, M.D., AMEDEO BONDI, JR., Ph.D., and  
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THE purpose of this paper is to present a serologically proved case of Q fever and reëmphasize the importance of considering this disease in the diagnosis of non-bacterial pneumonias. This case is of further interest because we feel that it is the first report of Q fever naturally acquired in Pennsylvania, as well as in eastern United States.

### CASE REPORT

W. W., a white male, age 36, was admitted to the Hahnemann Hospital February 9, 1948, complaining of chills and fever of one day's duration. The patient stated that he had felt well until 7:00 p.m., February 8, 1948 when he experienced a sudden chill which lasted the entire evening. He was awakened at midnight with chills and tried to keep warm by covering himself with additional blankets but to no avail. On arising at 6:00 a.m. on the ninth, he ached all over but decided to go to work. The patient worked at his job in a wool-processing factory until 3:00 p.m. when he was forced to leave because of generalized weakness and aching. Towards evening he became chilly again and feverish. A slight productive cough was present consisting of white phlegm. At no time was the sputum blood tinged. At the time of admission the same evening he complained of a headache and pain in the back and left chest, this latter pain having no relation to respiration. The history was negative for hemoptysis, chronic cough, dyspnea, night sweats and weight loss.

The past history was essentially negative except for an attack of "flu" in 1918; appendectomy, 1936; and a nasal operation, 1938.

Physical examination revealed a well developed young adult male. He was well oriented but appeared acutely ill with a red flushed face and hot dry skin. There was no evidence of dyspnea, cyanosis, edema, pallor, jaundice or glandular enlargement. The temperature was 103.2° F., the pulse 100, the respirations 20 and the blood pressure 140 mm. Hg systolic and 84 mm. diastolic. The nasal mucosa was injected and a mucopurulent discharge was present. Marked injection of the throat, and a post-nasal discharge were observed. Examination of the lungs failed to demonstrate any consolidation, râles or other abnormalities. The remainder of the examination was essentially negative. A persistent headache prevented him from sleeping. The patient was given 30,000 units of crystalline penicillin G in aqueous solution intramuscularly every three hours; 0.6 gm. of aspirin was also given.

On awakening February 10, 1948, he again complained of a headache and sore throat accompanied by a chilly feeling and general aching. Saline throat irrigations and neosynephrine 0.25 per cent three drops in each nostril every four hours were ordered. That afternoon the patient had a chill and became very toxic with increase

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in the severity of the headache. Examination revealed a markedly reddened pharynx. There were increased breath sounds at the left lung base and questionable tubular-like breath sounds at the right base. The roentgenogram of the chest was reported as "some accentuation of the bronchovascular shadows throughout the mesial aspect of both lung fields." Codeine sulfate, 0.3 gm., was given to control the headache. Profuse sweating developed and coughing increased. The dosage of penicillin was raised to 50,000 units every three hours.

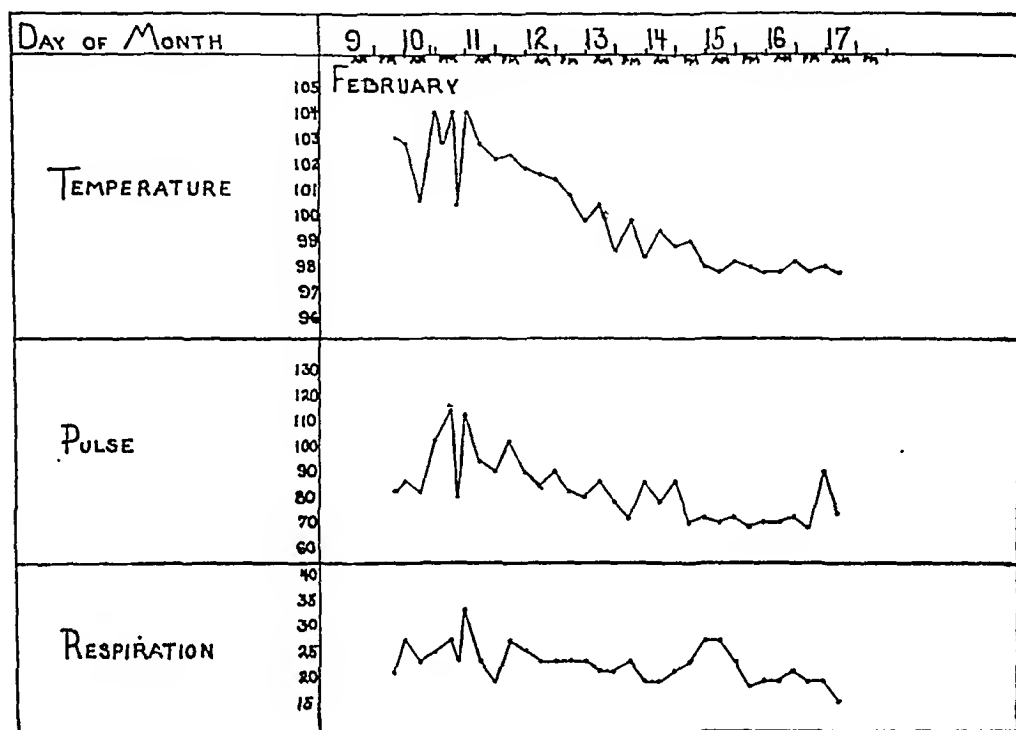


FIG. 1. Clinical chart.

The patient remained acutely ill for the next two days; physical findings remained essentially unchanged except for the presence of a few coarse râles throughout both the lung fields which cleared for the most part after coughing.

On February 13, a considerable improvement in the patient's condition was observed. His headache diminished in severity and finally disappeared. The inflammation of the pharynx began to subside; all lung fields were clear to auscultation and the temperature had begun to fall. From this day until his discharge on February 17, 1948, clinical improvement both objectively and subjectively proceeded rapidly, the temperature falling by lysis and reaching normal by the fifteenth. At the time of discharge, the patient ate well, had no headache, pains or cough.

The total dosage of penicillin administered from February 9 to February 16 was 2,580,000 units without apparent benefit to the patient.

#### LABORATORY FINDINGS

Urinalysis on admission was negative. Blood studies revealed a red cell count of 4,280,000, hemoglobin 13.7 gm., white cells 5,000 with 80 per cent polymorphonuclear cells and 20 per cent lymphocytes. Throughout the illness the

blood picture remained more or less constant. The electrocardiogram was normal. Bacteriological studies of the throat failed to demonstrate a pathogenic organism at any time. The spinal fluid study was normal. Stool examination was negative for occult blood, ova and parasites. The blood urea nitrogen and blood sugar were normal. Wassermann and Kahn tests of blood and spinal fluid were negative. Agglutination tests with the typhoid O and H, paratyphoid A and B, *Proteus* OX 19 and *Br. abortus* were negative.

Tests on the patient's sera taken shortly after onset and at several intervals during the course of the disease as well as following recovery were carried out at the Virus Diagnostic Research Laboratory at the Children's Hospital of Philadelphia. These consisted of: Complement fixation tests with the antigens of influenza virus types A and B, as well as the tests used routinely by this laboratory for the diagnosis of atypical pneumonia, i.e., complement fixation with an antigen of the psittacosis-lymphogranuloma group of agents and the antigen of Q fever rickettsia (American strain) and the cold agglutination test. The results are tabulated below.

Date	Influenza A	Influenza B	Psittacosis-L.G.V.	Cold Agglutinins	Q Fever
Feb. 11	<1:4	<1:4	<1:10	1:80	<1:2
Feb. 17			<1:10	1:80	1:16
Feb. 18	<1:4	<1:4		1:80	1:16
May 13					1:256
June 8					1:256*

\* This result obtained with the American strain of Q fever rickettsia was confirmed by Dr. H. Koprowski of the Lederle Laboratories using the Italian strain.

The results above reveal that the patient developed antibodies against the rickettsia of Q fever and not against the pneumotropic viruses. The presence of cold agglutinins is not considered significant since they were present in the serum taken three days after onset and since they failed to rise in titer. The finding of an increasing titer of antibodies to the Q fever rickettsia established a definite diagnosis of Q fever.

#### COMMENT

The significant clinical features of this case were: The explosive onset with chills, headache of such severe and persistent character that the diagnosis of meningitis was entertained, marked upper respiratory manifestations with minimal clinical and no roentgenological evidence of lung involvement. The course was a febrile one with a fastigium of temperature between 101° and 104° F., which fell spontaneously by lysis and was unaffected by penicillin. The white cell count remained normal throughout.

The above clinical findings initially suggested the diagnosis of an atypical pneumonia or influenza, but the course and subsequent clinical findings failed to support a diagnosis of the former; although in retrospect they were compatible with what other authors have described in proved cases of Q fever. This illustrates the need for laboratory aid in differentiating the etiological entities grouped clinically under the heading influenza, grippe or atypical pneumonia.

The signs, symptoms and roentgen-ray findings of Q fever described in the outbreak at the National Institute of Health<sup>1</sup> were those of atypical pneumonia.\* Atypical pneumonia also constituted an important feature of the first proved infection that was acquired naturally in the United States,<sup>2</sup> and in the various groups of cases studied by the Army<sup>3</sup> as well as the Amarillo epidemic.<sup>4, 5, 6</sup> Pulmonary lesions, however, have not been observed as a prominent feature of Australian Q fever.<sup>7</sup> Recent literature<sup>4, 8, 9, 10, 11</sup> has revealed the increasing incidence of Q fever in circumscribed areas of western, midwestern and southwestern United States. So far this infection has seemingly been found chiefly in packing house and slaughterhouse workers; dairy farmers and laboratory personnel. Isolated cases in all instances could be traced to exposure in a known endemic area.<sup>12</sup> Although it is an accepted fact that the organism, *Rickettsia burneti*, is present in the feces of certain arthropod vectors,<sup>13, 14, 15</sup> the actual method of transmission of the disease to man is uncertain.<sup>16</sup> There was a history of tick bite in some American cases that developed in areas where the rickettsia of Q fever has been found.<sup>17</sup> Careful epidemiologic studies carried out during the Amarillo, Texas epidemic<sup>4, 5, 6</sup> and elsewhere,<sup>12</sup> inconclusively attribute the acquisition of the infection to inhalation of contaminated dust. Of considerable interest is the occurrence of a number of proved cases of Q fever in the vicinity of Los Angeles, California and the isolation of the etiological agent from raw milk.<sup>8</sup> Although the rickettsia were recovered from raw milk, the available evidence failed to implicate the drinking of the milk as the cause of the infection. Huebner and his associates, however, believe that infected milk may serve as a source of infection by some mechanism not yet known.

The mode of infection in our patient is not certain. However, it is known that he handled wool and animal hair in a dusty atmosphere, and that subsequently other cases of Q fever were found in the same factory.<sup>18</sup> Thus it seems probable that the infecting agent was carried by these materials and entered through the respiratory tract.

The case is of importance in emphasizing the need for an accurate diagnosis of the etiology of influenza-like illnesses, or atypical pneumonia, particularly in view of the recent advent of antibiotics effective against rickettsia.<sup>19, 20</sup>

### SUMMARY

The first report of a serologically authenticated case of naturally acquired Q fever in eastern United States is presented. The clinical features are discussed in detail with emphasis placed on the consideration of this disease in the differential diagnosis of respiratory disorders. The possible mode of transmission is discussed.

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\* Aware of the fact that pulmonary infiltration occasionally occurs late in this infection, subsequent roentgen-rays were done on this patient and were found to be normal.

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## DIFFUSE MELANOSIS, PERICARDIAL EFFUSION, AND MELANURIA ASSOCIATED WITH MALIGNANT MELANOMA: CASE REPORT WITH AUTOPSY FINDINGS \*

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THE literature pertaining to malignant melanoma is voluminous. The following case is reported because of its unusual association of diffuse melanosis

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of the skin, cardiac metastases, massive pericardial effusion, and melanuria in the same patient, all secondary to a melanoma on the forearm.

#### CASE REPORT

F. R., a 47 year old American-born laborer and hide-sorter, entered the hospital on June 30, 1946, because his face "was turning all kinds of colors." Eight months prior to admission a flat mole the size of a dime on his right forearm had begun to enlarge and become blacker. In March, 1946, he had noted a lump in his right axilla. Hospitalization was advised by his doctor at that time but refused by the patient. Meanwhile, the mole on his arm continued to enlarge. Three or four weeks before entering the hospital he had noticed multiple subcutaneous nodules and increasing pigmentation of the face, neck, and hands. Dyspnea on exertion, hemoptysis, anorexia, and a weight loss of 10 pounds had also occurred during this time. His urine had become dark brown in color.



FIG. 1. Primary lesion on forearm, subcutaneous metastases, and melanosis of face and neck.

Prior to the present illness he had always been in good health. He had consumed about one quart of beer daily during the past few years. There was no history of his using any silver preparations or of any recent exposure to the sun.

Physical examination revealed an emaciated, poorly-developed white man, temperature 100° F., pulse 100, respirations 20. His face and neck were a bluish-black gun-metal color, fading to a light brown over the upper extremities and trunk, then to a normal color over the lower trunk and lower extremities. There were multiple hard subcutaneous nodules scattered over the entire trunk and both arms; these appeared to have a black color where near the surface. One nodule had broken through the skin on the anterior left thigh just below the inguinal ligament to form an oval, flat, black papule, 1 cm. in diameter. On the right forearm there was a large fungating black mass about 5 cm. in diameter and 3 cm. above the surface of the skin. The surrounding area was brownish-black in color for one-quarter to one-half inch about the base of the lesion. The mass was friable, grossly infected, and bled easily, although not appearing painful (figure 1).

The sclerae had a brownish tinge. Funduscopic examination revealed no abnormalities. The mucous membranes of the mouth and nose had a bluish-brown color. The teeth were carious, with somewhat hypertrophied gums, also bluish in color. The drumheads appeared normal. The neck veins were distended; there were stony hard nodes in the cervical and both supraclavicular regions. Similar nodes were evident in both axillary and inguinal regions. The chest was clear except for a few moist râles audible over the right middle lobe. The heart did not appear enlarged at this time. The rhythm was regular, the tones were of good quality, and no murmurs were audible. Blood pressure was 126 mm. Hg systolic and 90 mm. diastolic. A hard tender liver edge was palpated three fingers' breadth below the right costal margin. The spleen was not palpable. A diagnosis of melanoma with generalized metastases was made.

*Laboratory Data.* The urine was dark brown, specific gravity 1.018, acid reaction, negative for albumin and sugar. There was a 4 plus positive test for melanin using ferric chloride. Microscopic examination revealed 2 to 3 leukocytes per high power field, a rare red blood cell and no casts. There were 8150 white blood cells per cu. mm. with a differential of 54 polymorphonuclears, four band forms, two eosinophiles, one monocyte, three basophiles, and 36 lymphocytes. Red blood cells numbered 4.0 million; the hemoglobin (Sahli) was 12.4 gm. The Wassermann test was negative. Blood urea was 30 mg. per cent, sugar 88 mg. per cent, icteric index 10. Total cholesterol was 138 mg. per 100 c.c. of serum, free cholesterol 78 mg., esters 60 mg. per cent. On July 19, blood sugar was 76 mg. per cent, plasma sodium 322 mg. per cent, and potassium 25 mg. per cent. On July 22, the thymol turbidity test was negative, total protein 4.4 gm. per 100 c.c. plasma, and alkaline phosphatase blood level 5.8 units.<sup>1</sup> Calcium and phosphorus levels were 11.6 mg. and 3.9 mg., respectively. A bromsulphalein test on July 23 was lost because of hemolysis.

*Course.* Proctoscopy on July 3 revealed no lesions or evidence of pigment deposition in the rectosigmoid.

Biopsy of the lesion on the right forearm was reported as follows: "Section of skin biopsy shows a malignant invading neoplasm made up of heavily pigmented, polyhedral, spindle cells invading the connective tissue. The nuclei vary markedly in morphology and staining, and in some instances the cells are so heavily occupied by melanin that the morphology cannot be distinguished." The histologic diagnosis was malignant melanoma.

Liver punch biopsy on July 8 showed swelling and vacuolization of the cytoplasm of the liver cells. In the pericentral zone area and in some of the Kupffer cells there was a light-brown pigment interpreted as melanin deposition in the liver.



Roentgen-rays taken on July 11 revealed enlargement of the cardiac shadow in all its diameters, with a configuration suggestive of pericardial effusion and evidence of metastatic lesions in both basilar lung fields (figure 2). There were no metastases to the long bones, but one suspicious area of decreased density was present in the skull.

It was observed that the cardiac dullness had increased to the left mid-axillary line, whereas the point of maximal impulse remained in the mid-clavicular line. The tones were of fair quality. Rotch's and Ewart's signs were negative; the pulse was not paradoxical. However, the neck veins remained distended and the liver was palpable three fingers' breadth below the right costal margin. One plus edema of the ankles was noted for the first time. Fluoroscopy and roentgenkymograms confirmed the impression of pericardial effusion. An electrocardiogram on July 12 showed a sinus tachycardia, rate 106, low voltage of ventricular complexes, low  $R_4$ , with

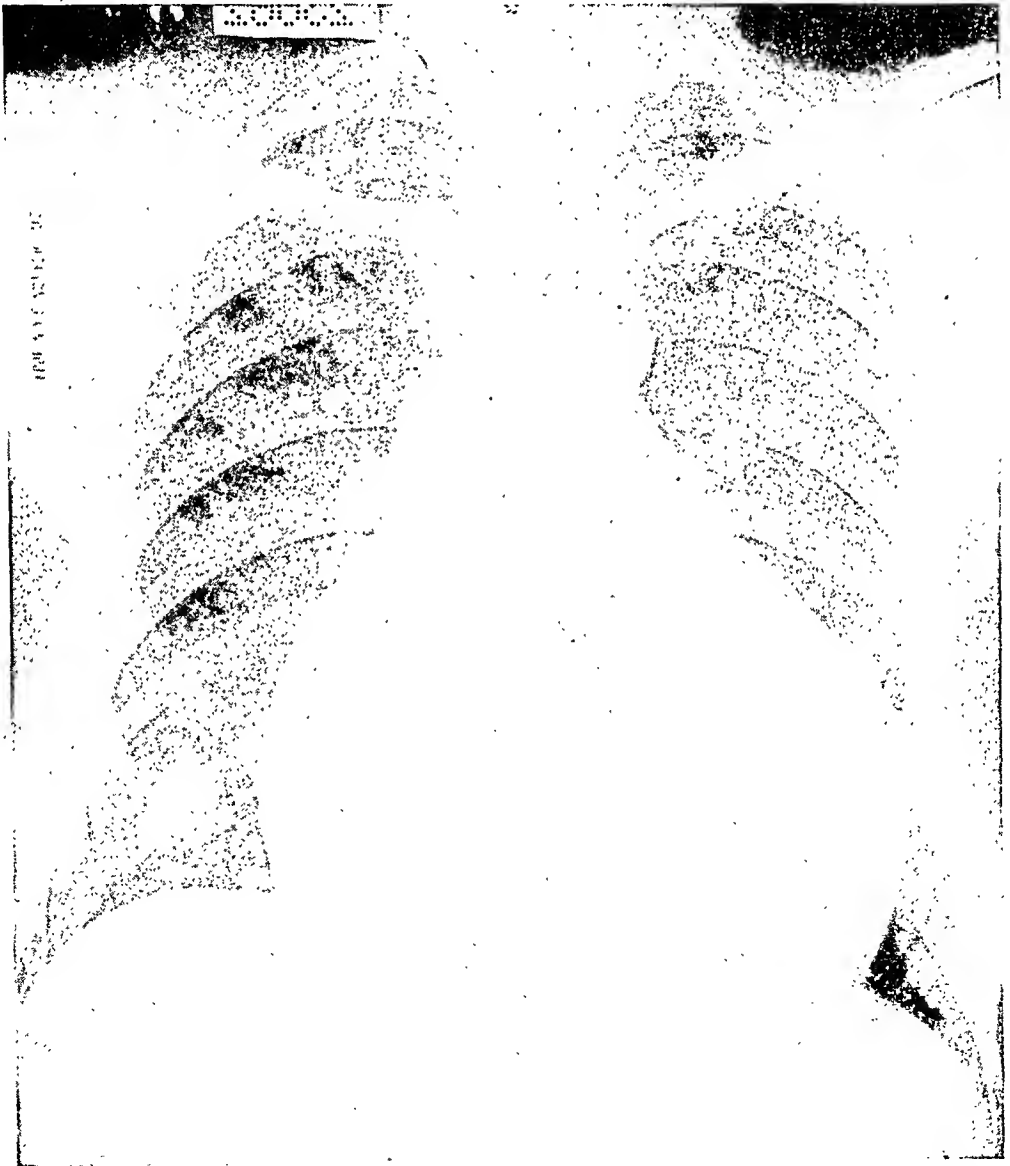


FIG. 2. Flask-shaped configuration of cardiac silhouette; metastases to lungs.

T-waves isoelectric in Leads I and IV ( $CF_4$ ) and semi-inverted in Leads II and III (figure 3a).

The patient began to complain of marked anorexia and substernal discomfort. Characteristically, he obtained some relief by leaning forward in bed.

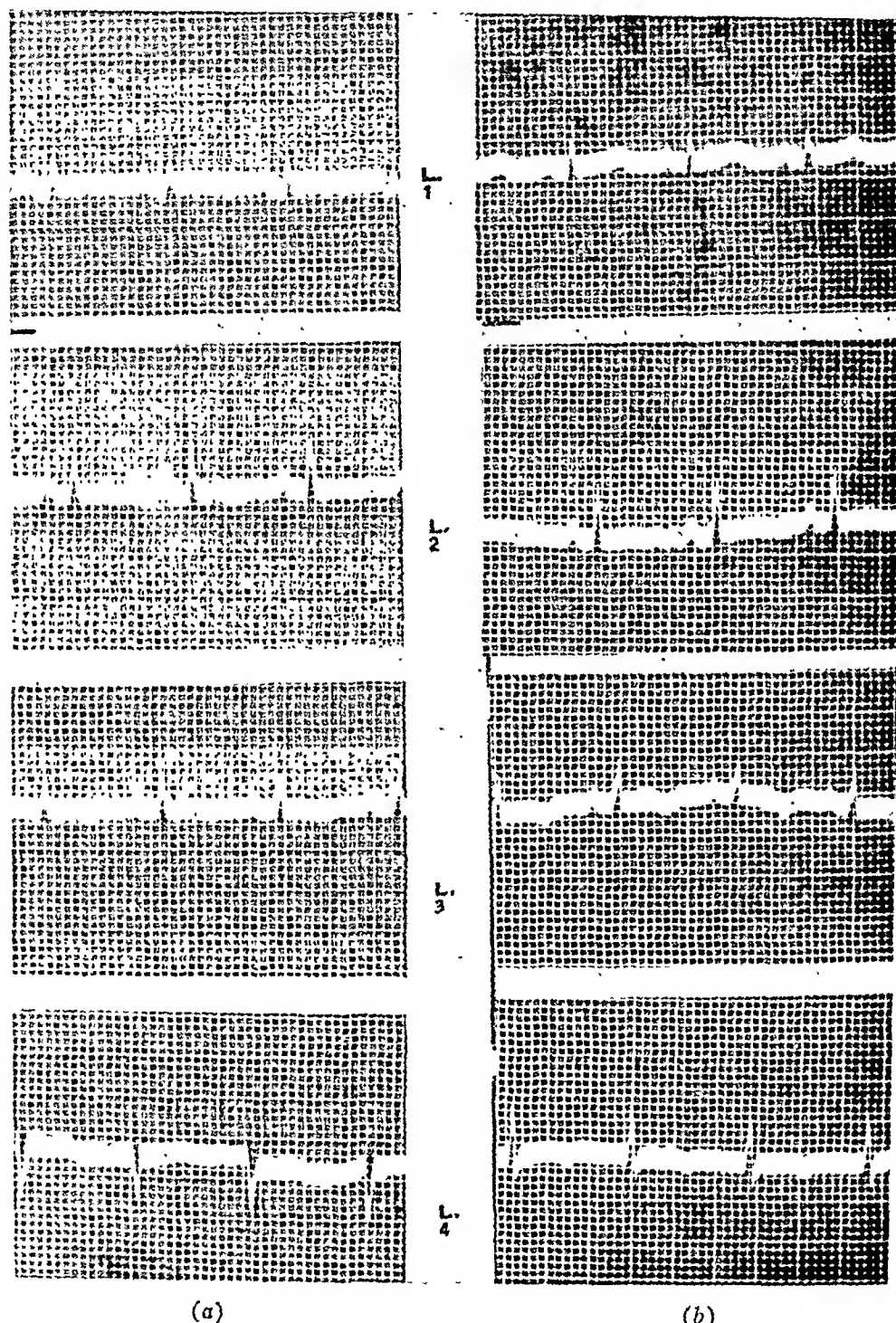


FIG. 3. Electrocardiograms (a) July 12, 1946. Low voltage of QRS complexes, low  $R_1$ ; isoelectric  $T_1$  and  $T_2$ ; semi-inversion of  $T_3$  and  $T_4$ . (b) July 27, 1946. Low voltage of QRS complexes; isoelectric  $T_2$ ; inverted  $T_3$  and  $T_4$ .

At this time the decholin circulation time was 23 seconds. The venous pressure was 21 cm. of water, rising to 24 cm. on liver pressure, and returning to 22 cm.

Pericardial tap was performed on July 19, by the left paraxiphoid approach, with the removal of 600 c.c. of a brownish-tinged, clear fluid. Blood pressure before the paracentesis was 111/98; immediately thereafter, it was 108/88. The patient experienced considerable relief. Dyspnea and edema decreased, and his neck veins became flat for the first time since admission. The fluid had a specific gravity of 1.009; there were 1800 cells per cu. mm., predominantly crenated red blood cells. A few polymorphonuclears and large macrophages containing brownish pigment were also present. The protein content was 980 mg. per 100 c.c. No malignant cells were noted in the cell block. The following day the patient appeared much improved. However, the liver did not recede; the spleen was palpated two fingers below the left costal margin for the first time.

On July 26, because of signs of increasing tamponade, pericardial tap was again performed. The blood pressure was now 94/80. Only 75 c.c. of slightly sanguinous fluid were withdrawn. A cell block of this fluid showed numerous polymorphonuclears, red blood cells, occasional lymphocytes and macrophages, and polyhedral cells containing dark brown pigment in the cytoplasm. The block was interpreted as positive for malignant cells.

A repeat electrocardiogram on July 27 again demonstrated low voltage of QRS complexes with isoelectric  $T_2$  and inverted  $T_3$  and  $T_4$ . The findings were compatible with pericardial involvement (figure 3b).

A third pericardial tap was carried out on July 29, when 750 c.c. of sanguinous fluid were removed through a needle inserted in the fifth interspace at the anterior axillary line and 300 c.c. of filtered air were injected. Blood pressure before the procedure was 92/84; immediately thereafter, it was 100/92. On the same day, because of signs of fluid in the chest, thoracentesis was performed in the ninth interspace in the midscapular line, and 650 c.c. of a sanguinous fluid similar in appearance to the pericardial fluid were obtained. Cell blocks of both fluids revealed no malignant cells; pigment laden macrophages were again seen. The patient obtained temporary symptomatic relief from these procedures but continued to go downward. Roentgen-rays of the chest on July 30 demonstrated a hydro-pneumopericardium and a left hydro-pneumothorax with well-visualized fluid levels.

The pericardial and pleural fluid rapidly reaccumulated. On August 1 the patient died.

*Urinary Studies.* A heavy black precipitate formed on the addition of ferric chloride or bromine water which could be dissolved by sodium carbonate solution and reprecipitated by the addition of acid, thus satisfying the criteria<sup>2</sup> for melanin.

The urine did not become dark on the addition of alkali, nor did it reduce Benedict's solution, ruling out alkaptonuria.

Thormählen's<sup>3,4</sup> test for melanin was strongly positive. This is performed similarly to the Legal test for acetone. A few drops of 5 per cent sodium nitroprusside are added to 3 to 5 c.c. of urine, and then a few drops of 10 per cent sodium hydroxide. At this point a deep ruby color results, which may also be given by acetone and creatinine. However, acidification with glacial acetic acid causes an immediate azure-blue color. Acetone, on the other hand, turns deeper red; creatinine turns yellow, then slowly green, and finally blue.

Estimation of the 24-hour output of melanin in the urine by the method of Blackberg and Wanger<sup>5</sup> on two successive days yielded 0.43 gm. and 0.47 gm. of melanin. This method is based on the precipitation of melanin from the urine, solution in 5 per cent sodium hydroxide, then reprecipitation with 0.1N HCl, filtering and weighing.

*Abstract of Autopsy Protocol.* The body is that of a white male measuring 67 inches and weighing approximately 115 lbs. The skin is dry and markedly pig-

mented, especially the facial and neck areas. Numerous small, firm, subcutaneous nodules are present, measuring 2 to 10 mm., many of which are fixed and attached to the underlying tissue. A large black fungating tumor mass is present on the anterior aspect of the mid-right forearm measuring 6 by 5 by 3 cm. The right sclera is mildly pigmented a light-brown color, but there is no evidence of jaundice or petechiae. The liver and spleen are palpable three fingers below the costal margins.



FIG. 4. Melanotic metastases to epicardium and myocardium.

On making the incision, there are numerous black, firm, discrete nodules seen throughout the subcutaneous tissue. The peritoneal serosal surfaces are smooth and glistening; there are tumor nodules throughout the abdomen, especially involving the peri-aortic lymph nodes. Numerous small, black, discrete nodules are present on both

pleural surfaces. About 500 c.c. of dark brown fluid are present in the left pleural cavity. Fibrous adhesions are noted at both apices. About 1000 c.c. of dark brown clear fluid are present in the pericardial sac. The pulmonary artery is opened in situ and no evidence of embolus is found.

The heart weighs 380 gm. The epicardium is studded with numerous black nodules varying up to 1 cm. in diameter (figure 4). Lying within the right atrium and its appendage is a large black friable tumor thrombus which is firmly adherent to the endocardial surface. The tricuspid orifice is almost occluded. At the apex of the left ventricle, a small firm adherent mural antemortem blood thrombus is present. The myocardium on cut section is pale red with diffuse brown speckling. Several small tumor nodules are noted scattered throughout the myocardium. The coronary arteries are patent (figure 5).

The lungs reveal dense fibrous adhesions at both apices. The left lower lobe is atelectatic as a result of fluid compression of the left pleural cavity. Scattered

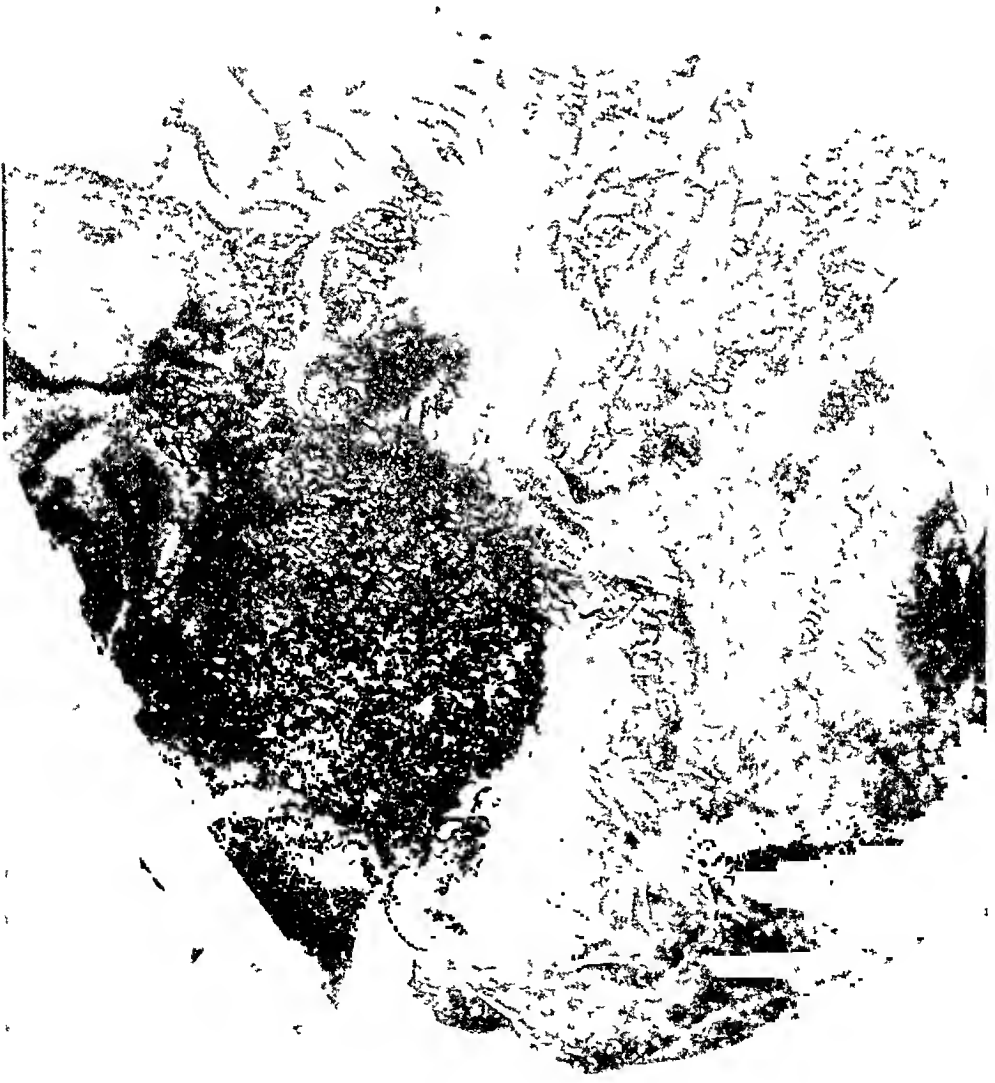


FIG. 5. Melanotic tumor thrombus in right atrium and appendage; metastases in myocardium.

throughout the lung parenchyma are numerous black, firm, discrete tumor nodules. The hilar, tracheobronchial, and para-esophageal lymph nodes are markedly involved by melanotic tumor.

The spleen weighs 1200 gm. It is black, firm, and almost entirely replaced by tumor.

The liver weighs 1800 gm. The edges are sharp and the organ is diffusely pigmented brown-black. On cut section, several tumor nodules are seen measuring from 8 to 13 mm. The liver is nutmeg in appearance and shows moderate edema of the parenchyma.

In place of the adrenals are two huge, friable, triangular black tumor masses measuring about 5 cm. by 5 cm. by 3 cm. On section of these masses, no gross evidence of adrenal tissue is seen.

The right kidney weighs 180 gm. and the left kidney 200 gm. Numerous tumor nodules are present in the capsule, which strips with ease. The kidney is diffusely pigmented. Tumor has invaded both renal veins.

The submucosa of the duodenum and entire small intestine is studded with small, black, discrete tumor nodules, 2 to 5 mm. in diameter.

The right sternal-clavicular joint on cut section is diffusely infiltrated with black melanotic pigment, but the ribs and vertebrae are grossly free. The remaining organs are not remarkable.

Permission for examination of the brain and spinal cord could not be obtained.

Microscopic examination confirmed the presence of metastases in the sites mentioned. There was diffuse infiltration of the liver and spleen by pigmented tumor cells; there was also considerable pigment in the reticulo-endothelial cells. In the kidney, pigment was laid down in a haphazard fashion, but mostly in the epithelium of the collecting and convoluted tubules, which showed cloudy swelling. Pigment-bearing cells were also noted in the diaphragm, prostate, and bone-marrow. There was no recognizable adrenal tissue in histological sections of the tumor masses replacing these glands. The skin of the abdomen showed no increase in melanin pigment; permission to study the skin of the face or neck was not granted.

*Anatomical Diagnosis.* Melanocarcinoma right forearm, with metastases to lungs, pleura, liver, heart, spleen, adrenals, small intestine, skin, subcutaneous tissue, muscles, bone marrow and paratracheal, hilar, parabronchial, axillary, cervical and inguinal lymph nodes; mural tumor thrombus right auricle.

Melanosis of skin, liver, lungs, heart, kidneys, spleen, adrenals, and intestine. Antemortem blood thrombus left ventricle (apex); left pleural effusion; pericardial effusion; chronic passive congestion of liver.

## MELANOSIS

Although melanoma is a fairly common clinical entity, diffuse melanosis of the skin is of infrequent occurrence. Diffuse melanosis, manifested by diffuse pigmentation, should be distinguished from massive discrete metastases to the skin. The cause of diffuse melanosis is not entirely clear, since there are cases of widespread metastatic involvement frequently seen which do not show melanosis. A patient described by Way and Light<sup>6</sup> manifested thousands of metastatic macules and papules, so numerous as to resemble a purpura hemorrhagica, with secondary skin pigmentation. There were a few small metastatic nodules in the left adrenal gland; the right was not involved. Odel, Montgomery and Horton<sup>7</sup> described a case of melanosis associated with melanuria secondary to a malignant mole over the left scapular region. Their patient had a diffuse blue-gray pigmentation of the skin and mucous membranes; the face was

a deep blue-black color. Dixon<sup>8</sup> also emphasized the "gun-metal or argyria-like color" of his patient. Odel et al. postulated a toxic or metastatic involvement of the suprarenal glands and adjacent chromaffin tissues; this was not proved, since no autopsy was obtained. In Dixon's case, there were minute islands of metastases in both adrenals. In a case of primary melanoma of the left adrenal recently described, there was no melanosis; however, the right adrenal contained only a small tumor nodule.<sup>9</sup> In the author's case, both adrenals were massively involved and almost completely replaced by tumor. No adrenal tissue could be identified microscopically. Nevertheless, as far as could be determined, there was no gross adrenal insufficiency. The blood sugar and plasma sodium were within normal limits; the plasma potassium was slightly elevated. However, even in Addison's disease, there is no constant correlation between degree of pigmentation and severity of systemic manifestations.<sup>10</sup> It is possible that the coexistence of severely damaged adrenals with excessive amounts of melanin in the body facilitates the deposition of pigment in the skin. The low blood pressure can be explained by the massive pericardial effusion. Further studies of adrenal function were unfortunately not undertaken.

The bluish color seen clinically in diffuse melanosis is thought to be due to the deposition of melanin in chromatophores in the corium with a relative absence of melanoblasts in the epidermis. The mechanism is comparable to that in *nevus blau* (blue nevus of Jadassohn), in which the pigment is mostly in melanoblasts in the cutis rather than in the epidermis. As noted by Odel et al.,<sup>7</sup> there may be accentuation of the pigmentation in exposed regions of the skin, particularly the face and neck. This was true in the case described here. Edwards and Duntley<sup>11</sup> have called attention to the rôle of light scattering in the production of skin coloration. The shorter wave-lengths towards the blue end of the spectrum are scattered laterally in the stratum mucosum and then partially reflected, whereas the longer red-wave lengths penetrate to the deeper skin layers, where they undergo partial absorption and partial reflection. When a large amount of melanin is present in the corium, these red rays are more completely absorbed and the blues thus predominate. Jeghers<sup>12</sup> has recently reviewed this subject in detail.

#### CARDIAC METASTASES

In regard to cardiac metastases from malignant melanoma, Moragues<sup>13</sup> reviewed the literature in 1939 and noted only 23 reported cases, plus four of his own. Scott and Garvin<sup>14</sup> reviewed a series of 1082 autopsies at the Cleveland City Hospital, 10.9 per cent of which, or 118, showed heart metastases. There were 10 melanomas in this group, five of which metastasized to the heart. Among the cases studied by Moragues at the St. Louis University Hospitals were seven melanomas, four of which developed cardiac metastases. It would therefore appear that melanomas frequently metastasize to the heart. However, massive pericardial effusion secondary to these cardiac metastases is of infrequent occurrence.

The patient described here probably had a small pericardial effusion which was not detected when he first entered the hospital. As the fluid increased, signs of increasing cardiac size and tamponade became evident. Despite tapping, the effusion rapidly reaccumulated. The first fluid withdrawn was a clear, brownish-tinged fluid with the characteristics of a transudate, although of malignant etiology. The fluid subsequently became more sanguinous in nature;



coincidentally, a sanguinous pleural effusion also developed. Hydropneumopericardium was induced to delineate the pericardium, as described by Fenichel and Epstein.<sup>15</sup>

The massive intracardiac and myocardial metastases were striking. Moragues<sup>13</sup> has described a case with a comparable degree of involvement in which a tumor thrombus extended from the right ventricle into the pulmonary conus, almost occluding it. Scott and Garvin<sup>14</sup> mention a case of melanosa of the eye with metastases to the left atrium, left ventricle and pulmonary conus who showed attacks of paroxysmal auricular fibrillation. In the present instance, despite the huge tumor thrombus in the right auricle, there was no clinical or postmortem evidence of blockage of the orifices of the great veins. However, the tricuspid valve was almost occluded. The electrocardiographic changes and clinical findings were principally those associated with pericardial effusion.

### MELANURIA

Eppinger<sup>16</sup> in 1910 postulated that melanin appears in the urine only when the liver has been extensively involved by melanotic metastases so that a functional insufficiency exists. Blackberg and Wanger<sup>5</sup> stated that melanuria is not noted unless metastases to the liver are present. However, in view of more sensitive concentration methods for detecting minimal amounts of melanin,<sup>4</sup> it is evident this premise must be reexamined. Moreover, melanuria has been reported in a great variety of conditions.<sup>2, 17, 18, 19</sup> There is no convincing evidence that melanuria is necessarily associated with impaired liver function. In the present study there was evidence of moderate liver damage. However, it is more probable that melanuria occurs when a threshold concentration of melanin bodies is exceeded in the body.<sup>4</sup>

Most of the usual clinical tests for melanuria depend upon the oxidation of a water-soluble colorless or light-colored precursor of melanin, melanogen, to melanin, in the form of a dark brownish-black precipitate. In far-advanced cases, the urine may be dark on passage and become still darker on standing.<sup>20</sup> This was true in the present instance. Melanin pigment may be deposited directly into the kidney tubules if the kidney itself is involved by tumor. Melanin in the urine must be differentiated from bile pigments, blood pigments such as methemoglobin, porphyrins, phenol oxidation products, and alkaptone bodies.<sup>2</sup> The latter may occur in the urine, together with melanin, as in the case reported by Swirsky.<sup>18</sup>

The reagents most often employed in testing for melanin are ferric chloride and bromine water. However, as Rothman,<sup>4</sup> who has studied this subject critically, and others<sup>5</sup> have pointed out, these tests are neither sensitive nor specific, and may yield confusing results in less obvious cases. Moreover, these are little more sensitive than simple darkening of the urine exposed to air. Rothman has found the Thormählen reaction much more satisfactory in that it is highly specific and about 50 times as sensitive as the oxidation tests. Ehrlich's aldehyde reaction is about twice as sensitive as the Thormählen reaction, but less specific for melanin.

The total amount of melanin excreted by this patient per 24 hours, as estimated by the method of Blackberg and Wanger,<sup>5</sup> was noted to be 0.43 gm. and 0.47 gm. on two successive days. This compares with a value of about 1 gm. in three days reported by Peters for a case of melanuria without melanosa.



This is also about the total estimated amount of pigment found in the skin and hair of a dark Negro,<sup>16</sup> indicating the large amount of pigment which may be formed by the body under pathological conditions.

### SUMMARY

1. A case of malignant melanoma manifesting diffuse melanosis of the skin, cardiac metastases, pericardial effusion, and melanuria is reported.

2. Diffuse melanosis associated with melanoma may be related to concomitant destruction of the adrenals, as noted in this case.

3. Cardiac metastases are frequently encountered secondary to malignant melanoma. Massive pericardial effusion may also supervene.

4. The pathogenesis and some of the clinical tests for melanuria are discussed; Thormählen's reaction is most satisfactory.

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## TRANSIENT RIGHT BUNDLE BRANCH BLOCK, WIDE S WAVE TYPE, IN WHICH NORMAL CONDUCTION OCCURRED BOTH SPONTANEOUSLY AND IN RESPONSE TO VAGAL STIMULATION \*

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IN routine electrocardiograms taken on healthy young adults without clinical evidence of heart disease, bundle branch block is a rare finding, occurring in less than 1 per cent.<sup>1, 2, 3, 4</sup> Apart from those cases falling into the special class described by Wolff, Parkinson and White, transient bundle branch block has been reported, with rare exceptions,<sup>5</sup> only in association with obvious heart disease clinically or in individuals in whom the age factor alone suggested the likely possibility of coronary sclerosis.<sup>6, 7, 8</sup> The presence of bundle branch block in a 28 year old soldier with a normal cardiovascular system clinically suggested the possible influence of primarily physiological factors. It was found that transient periods of normal conduction occurred on several occasions in response to stimuli considered to act through vagal centers. Spontaneous reversion to normal conduction was noted only once. It is of some interest that attention has been called to the fact that this type of bundle branch block is less often associated with serious heart disease.<sup>9, 10</sup>

### CASE REPORT

C. J. D., a 28 year old infantryman, was admitted to an Army General Hospital on June 1, 1945. His family history was negative, his birth had been normal, and his general health during infancy and childhood was apparently excellent. At the age of 11, because of a sore throat and rash he was admitted to the Charles V. Chapin Hospital in Providence, Rhode Island. While under observation for a period of four weeks no signs suggesting rheumatic fever or diphtheria or any evidence of cardiac dysfunction were noted in the hospital record. Other childhood diseases were denied. He remained in excellent health through four years of college and one additional year at a Catholic University prior to induction into the U. S. Army in July 1942. Basic infantry training was completed without any physical difficulties or complaints and in December 1942 he was ordered to an Officers Candidate School, but "washed out" after eight weeks for non-medical reasons. He continued in good health and in February 1944 went overseas. In June 1944 he first noticed the onset of fleeting arthralgias in the left great toe, left knee, metacarpal phalangeal and interphalangeal joints of the left hand. Concomitantly he developed a chronic head cold without sore throat or fever but accompanied by moderate mucopurulent nasal and postnasal discharge, and a cough productive of small amounts of purulent sputum in the morning which was blood streaked on one occasion. For this he was admitted to an Army General Hospital and observed for three weeks. At no time was he febrile, nor were the joint pains ever accompanied by objective signs. His "sinuses were washed out once" and "special roentgen-rays" (apparently bronchograms) taken prior to discharge to duty. By that time the respiratory symptoms had subsided, and except for mild arthralgias localized as described above, occurring at irregular intervals, he felt well and remained so through the rest of the summer. In December 1944 he was transferred to France for further combat infantry training. The arthralgias subsided at this time except for very occasional mild pains in the left knee. In March 1945

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just before going into combat he developed an acute psychosis and was returned to another Army General Hospital for treatment. Upon his arrival there his physical examination was negative and his general condition, except for his mental state, was good. In the course of obtaining medical clearance for insulin shock therapy a routine electrocardiogram was obtained. Both the one taken on April 25 and a repeat tracing on April 26 recorded persistent right bundle branch block. The cardiac examination was otherwise negative. In view of this finding shock treatment was considered inadvisable.

He was evacuated to the United States and admitted to an Army General Hospital on June 1, 1945, as a closed ward patient. Within two weeks his psychiatric condition had improved considerably and he was soon transferred to an open ward. His physical condition continued excellent. He ate well and was afebrile. The system review throughout the time of his admission was negative except for an occasional "sticking pain" located below and outside the cardiac apex. This pain was described as "coming on like a shot and going as fast." It occurred about once a week and more frequently at rest than when active. He admitted having first felt this pain while at Officers Candidate School in 1942, more frequently after arriving in England in 1944, and less often since then. This complaint had never interfered with his activity. There were no other cardiac symptoms. The patient neither drank nor smoked. He remained under observation and treatment until October 4, 1945.

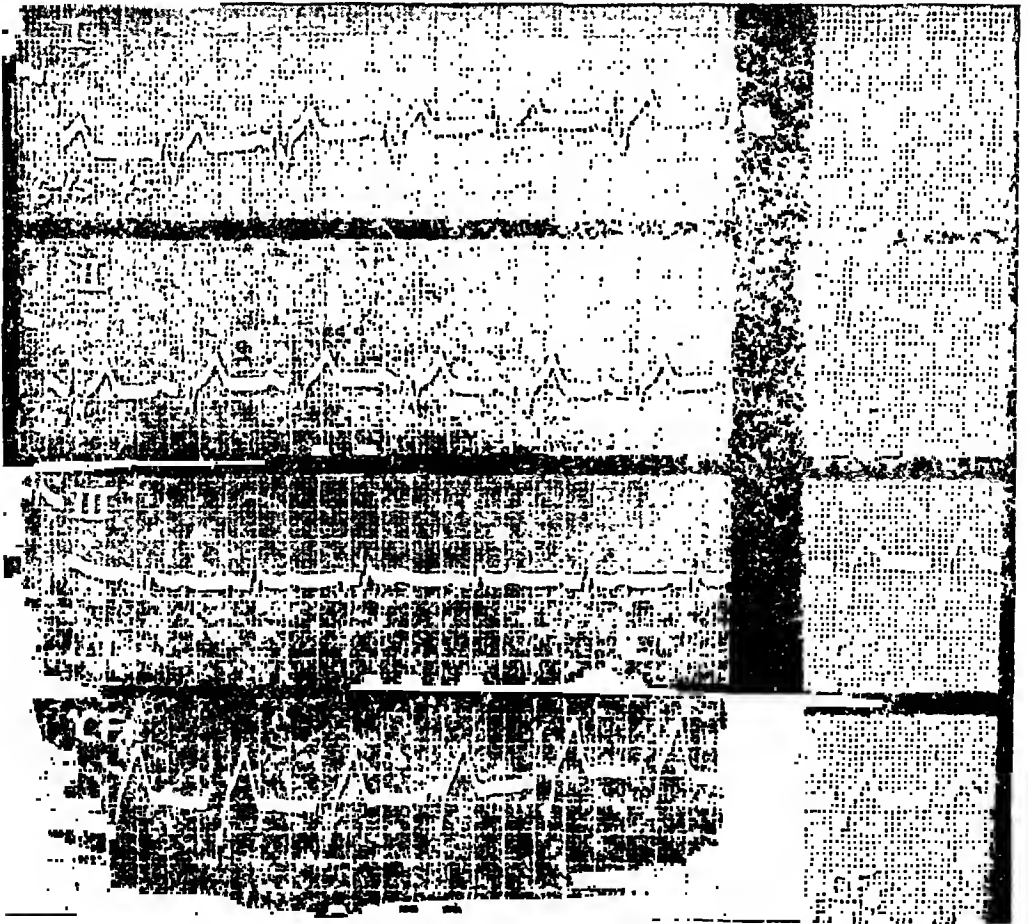


FIG. 1. Routine electrocardiogram taken on June 15, 1945. . Right bundle branch block with a wide S wave pattern. Rate 83. P-R interval .13 sec. I-V conduction time, .11 to .12 sec.

*Physical Examination.* The patient was a quiet, passive, emotionally immature young man appearing younger than his stated age. He was of medium height and build. The general physical examination was not remarkable. The eye grounds were normal. The tonsils were small and not inflamed. There was no evidence of an active sinus infection. The lungs were clear and the abdomen was negative. The extremities were normal and the radial, posterior tibial, and dorsalis pedis vessels were soft with good and equal pulsations bilaterally. There was no evidence of unusual vasomotor activity. The pulse rate was 79 and the rhythm was regular. The blood pressure was 110 mm. Hg systolic and 78 mm. diastolic. The point of maximum impulse was in the fourth interspace 2 cm. inside the nipple line. The heart sounds were not remarkable and there was no splitting or reduplication of the first sound at the apex. In the supine position there was a soft grade 1 blowing systolic murmur audible at the apex but heard more easily in the third left interspace 2 cm. to the left of the sternal border. It disappeared when the patient assumed the sitting or standing position. The murmur was not transmitted to the axilla or lung bases posteriorly. After running in place for one minute (approximately 187 steps) the heart rate increased from 79 to 140 per minute and the respiratory rate from 16 to 28 per minute. Following cessation of effort the heart rate noted at one, two, three and five minute intervals was 110, 100, 94, and 82 respectively. The patient did not complain of dyspnea, palpitation or cardiac pain. No change was noted in the quality or intensity of the systolic murmur.

*Laboratory Data.* The complete blood count and urine examinations were not remarkable. The stool was negative for ova and parasites. The Kahn reaction was negative. Repeated erythrocyte sedimentation rates (Wintrobe) were all below 8 mm. per hour. Blood chemistry findings included the following: Non-protein nitrogen 30 mg. per cent, fasting blood sugar 91 mg. per cent, cholesterol 165 mg. per cent, phosphorus 3.5 mg. per cent, calcium 10.5 mg. per cent, and serum proteins 6 gm. per cent with an A/G ratio of 1.5/1. A roentgenogram of the chest was negative. A tele-roentgenogram showed the heart to be small but within normal limits according to the Unterleider tables. Fluoroscopy of the heart with barium swallow revealed no abnor-

TABLE I  
Showing the Dates on Which Observations Were Made and the Effect  
of Various Procedures on Intraventricular Conduction

Date	6-18/45	6-28/45	7-15/45	7-20/45	8-6/45	8-15/45	8-20/45	8-27/45	9-12/45
Control period	0	X	0	0	0	0	0	0	0
Controlled breathing alone		X	0	0	0	0	0	0	0
Changes in position			0	0	0				0
Carotid sinus stimulation			X	0	0	0	0		
Atropine early effect 10-15 min.	X	X	X				0*		X
Atropine late effect after 30 min.	0	0	0				0		0
Oxygen						0			
Amyl nitrite						0			
Errotamine					0				
Pro-tigmine								0	

0—No change, persistent right bundle branch block.

X—Periods of transient reversion to normal I-V conduction noted.

\*—On this occasion the dose of atropine was increased to 2.5 mg.

malities of the heart, lungs or great vessels. An electrocardiogram taken on June 15, 1945 recorded right bundle branch block with a wide S wave pattern. The P-R interval was .13 to .14 second and the interventricular conduction time .11 to .12 second (figure 1). Although the history raised the possibility of an episode of rheumatic fever in the past it was the opinion of the author that the evidence for this diagnosis was insufficient. The possibility of the murmur being related to a congenital lesion was also considered but as the murmur fulfilled the usually accepted criteria of a "physiological murmur" and the rest of the examination was negative this diagnosis also seemed unwarranted.

*Course.* During the four months of the patient's admission his electrocardiogram was followed at length on nine occasions (table 1). On each, prior to observing the effect of a drug, any maneuver or series of maneuvers, Lead II was observed for 20 to 30 minutes with the patient resting in the supine position to establish a base line. All tracings illustrated were taken with the subject supine. Changes in position, where noted, include approximately five minutes of observation in the right and left

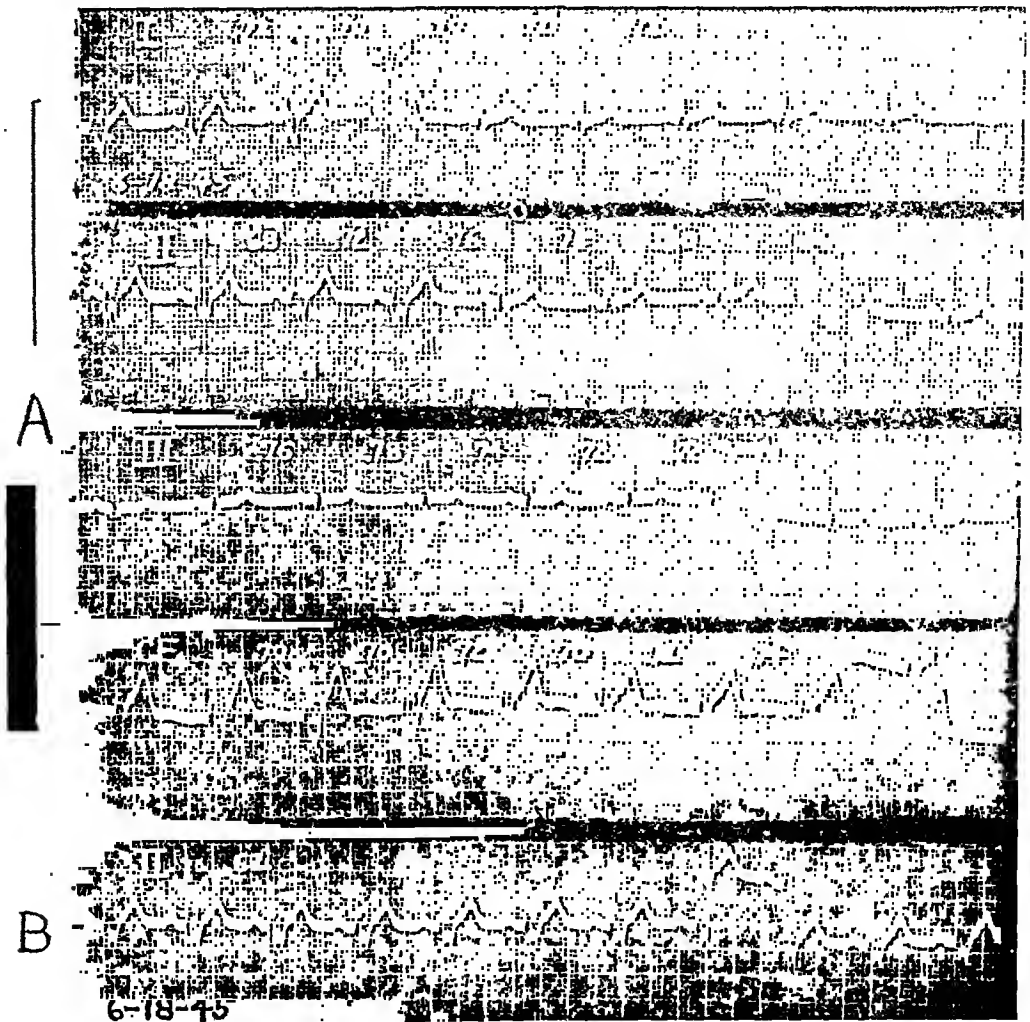


FIG. 2. *A*, June 18, 1945. Electrocardiogram taken 15 minutes after the subcutaneous injection of 1.5 mg. of atropine sulfate showing transitions from right bundle branch block to normal conduction in all leads but III. *B*, a portion of Lead II taken 15 minutes after *A* showing persistent right bundle branch block. Time intervals between complexes where noted are in tenths of seconds.

lateral, sitting and standing positions. After the vagal effect of controlled breathing was first observed on June 28 it was used subsequently when studying the effect of each drug or maneuver with the thought that it might reinforce any tendency to change. In each instance the patient was directed to take a maximum breath quickly, hold it for a moment, then expire naturally not forcibly.

The various occasions on which observations were made are not described in chronological order as listed in table 1, but are grouped otherwise for brevity and simplification.

The response to atropine sulfate was observed on four occasions. On three of these during the eight to 15 minute period following the subcutaneous injection of 1.5 mg. of the drug abrupt transitions from right bundle branch block to normal conduction for variable periods were recorded (figures 2 and 3). The intervals of normal conduction covered a single or multiple complexes. The largest number of successive normal complexes recorded was 34. When a tendency to sinus arrhythmia was present and particularly when it was enhanced by controlled breathing during the eight to 15 minute interval, transition to normal conduction occurred with the onset of expiratory slowing and lasted until the next inspiration began (figure 3 c, d, and e).

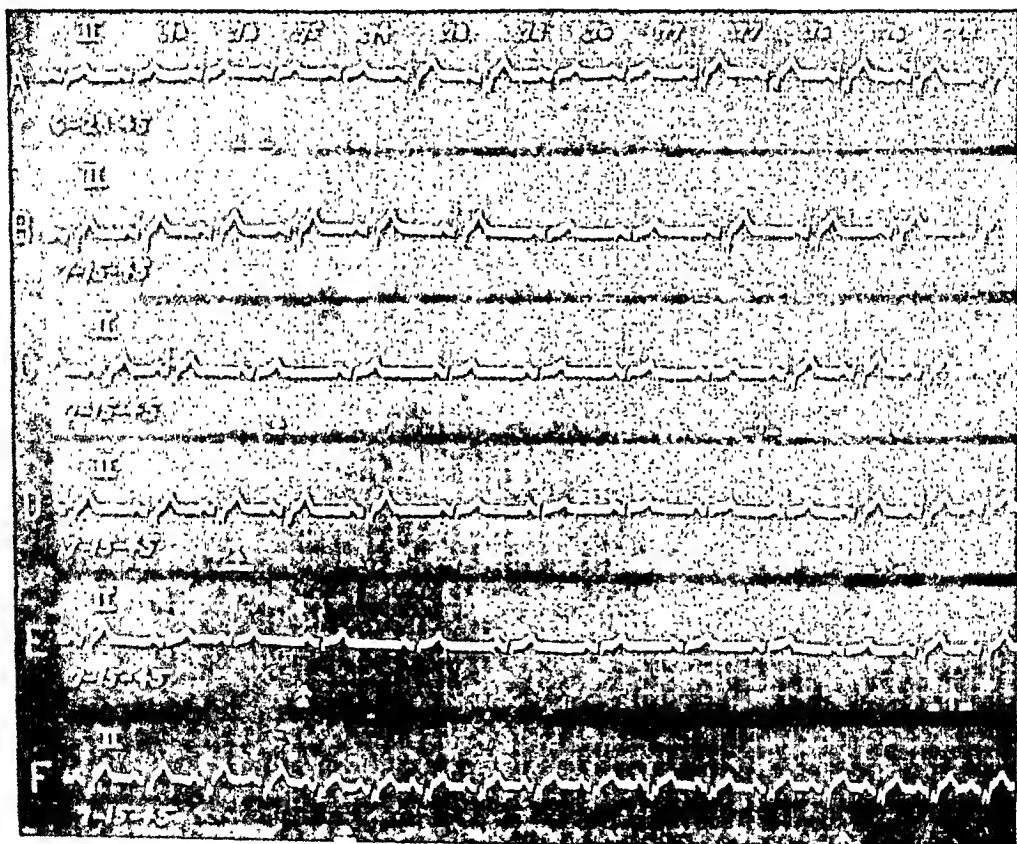


FIG. 3. *A*, June 28, 1945. Sample of Lead II taken during the 30 minute control period showing spontaneous transitions to normal conduction. *B*, August 15, 1945. One of two pairs of normal complexes occurring during left carotid sinus stimulation. *C*, *D*, and *E*, July 15, 1945. The effect of three successive breaths during controlled breathing observed in the 10 to 15 minute period following 1.5 mg. of atropine. One tap on the lead indicator marks the height of inspiration and two taps the end of the succeeding expiration. *F*, a portion of Lead II taken 15 minutes after *C*, *D*, and *E*, recording the increase in rate, disappearance of the response to controlled breathing and return of persistent bundle branch block. Time intervals between complexes where noted are in tenths of seconds.

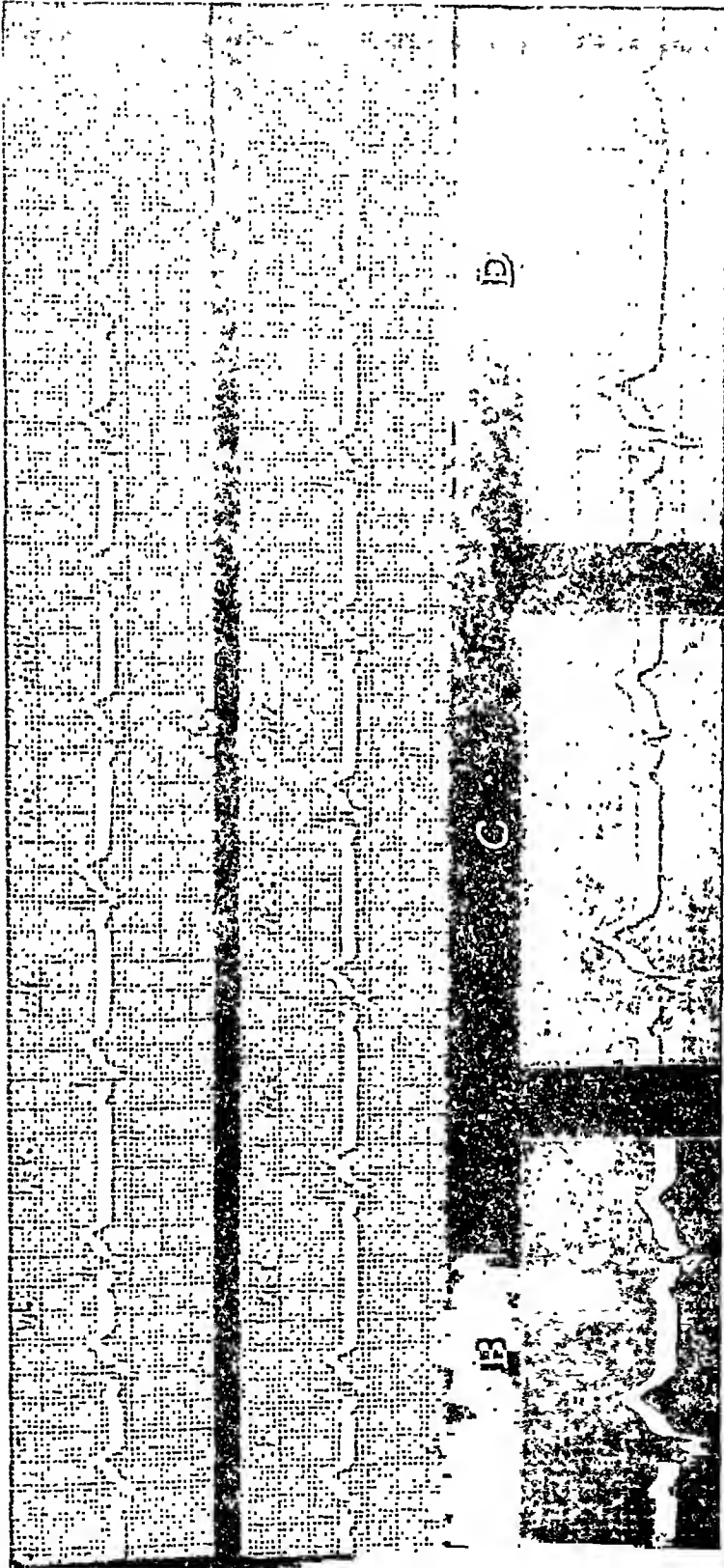


FIG. 4. A, August 6, 1945. Samples of Lead II during two successive breaths 30 minutes after the subcutaneous injection of 0.5 mg. of ergotamine tartrate recording a marked sinus arrhythmia in response to controlled breathing and persistent right bundle branch block. B, C, and D, magnifications of the recorded abrupt reversion to normal conduction as it occurred, B, spontaneously on June 28, 1945, C, during left carotid sinus stimulation on July 15, 1945, and D, during the 10 to 15 minute period following atropine on September 12, 1945. Time intervals where noted are in tenths of seconds.



Although reversion to normal conduction could be regulated during this period by controlled breathing this maneuver was not necessary for transition to occur. Reversion otherwise was unpredictable and did occur without any significant change in rate as recorded in Leads I and 4F of figure 2. Eighteen minutes after the injection no normal complexes were noted on any occasion. At this point the parasympathetic effect of atropine became evident, the rate increased to between 90 and 100, and the response to controlled breathing disappeared (figure 2).

On one occasion when the dose of atropine was increased to 2.5 mg. (August 20, 1945), transition to normal conduction was not noted during the eight to 15 minute period following the injection.\* Although very slight slowing was observed during the expiratory phase of controlled breathing it was transient and soon followed by a persistent tachycardia.

Spontaneous reversion to normal conduction was observed only once on June 28 (figure 3a). The number of successive normal complexes varied from one to 17. These occurred throughout the control period, tending neither to increase nor decrease. No significant sinus arrhythmia was present and the occurrence of normal or blocked complexes bore no definite relation to what slight variations in rate existed. The subcutaneous injection of 1.5 mg. of atropine sulfate was not followed by an increase in the number of normal complexes during the eight to 15 minute period following the drug. It was first noted on this occasion that transient reversion to normal conduction could be regulated by controlled breathing. After 20 minutes the parasympathetic effect of atropine was evidenced by a fixed rapid rate and normal complexes were no longer observed.

The effect of pressure on the left, right and both carotid sinuses in the standing and supine positions was observed on four different occasions. Transition to normal conduction was noted only once (figure 3b), during left carotid sinus pressure, and consisted of two pairs of normal complexes.

Changes in position observed on four occasions, the administration of 100 per cent oxygen through a BLB mask for five minutes, the intramuscular injection of 2.5 mg. of prostigmine and the inhalation of amyl nitrite (0.32 c.c.), each observed on one occasion, had no effect on the bundle branch block.

Although the intramuscular injection of 0.5 mg. of ergotamine tartrate resulted in the most marked sinus arrhythmia in response to controlled breathing, no effect on the bundle branch block was noted (figure 4).

## DISCUSSION

It is generally accepted that bundle branch block can occur in the absence of a demonstrable histological lesion. Transient bundle branch block has been reported in congenital heart disease, and associated with diphtheritic myocarditis, chronic rheumatic heart disease with and without active rheumatic infection, thyrotoxicosis, hypertension and arteriosclerosis, and with coronary sclerosis with and without myocardial infarction. In these instances a degree of temporary impairment in the metabolism of that part of the bundle branch system which would depress conduction sufficiently to produce the particular effect was generally hypothesized as the most reasonable explanation of the phenomenon. Transient bundle branch block has also been reported during quinidine adminis-

\* It is generally accepted<sup>24, 25</sup> that small doses of atropine stimulate and do not paralyze the vagus. The dosage level above which paralysis can generally be expected to occur is about 2.0 mg. Dosages of 2.5 mg. have been noted, however, to be followed by short periods of vagal stimulation before the effects of paralysis became evident.<sup>12</sup> It is apparent that not only the size of the dose but also the time of action as well as the subject's individual tolerance must be taken into consideration before evaluating the effect of a given dose.



tration in the treatment of heart disease. In general, conduction was observed to improve or return to normal with improvement in the cardiac status. The fact that pathological processes are not necessarily permanent and that abnormal physiological states may precede eventual pathologic responses has been emphasized as an important consideration in evaluating the significance of transient bundle branch block, and is supported by clear cut evidence of cardiac disease in all but an exceptional case.<sup>8</sup> In certain instances, however, one is led more forcibly to seek other possible explanations. Although underlying pathologic lesions cannot be ruled out in the case presented here, there is nothing save the conduction abnormality to suggest their presence. "Fatigue" of a pathologically depressed bundle branch, if it cannot be eliminated as a contributing factor, would hardly seem to be of much significance. None of the factors potentiating myocardial fatigue were present and normal conduction was observed to occur transiently without any change in rate both spontaneously and during the period of early atropine effect. It also was not observed when the slowest rates noted were induced by controlled breathing following ergotamine.

More interest has been directed recently to the effects of postural and respiratory maneuvers, carotid sinus stimulation, and various autonomic drugs on certain phases of cardiac conduction.<sup>4, 11, 12, 13, and 14</sup> Techniques employing these effects have been utilized in evaluating the significance of abnormalities in A-V conduction and the form, amplitude and polarity of T-waves in both the limb and chest leads.<sup>13, 14, and 16</sup> The importance of autonomic controls as contributing influences on these phases of the electrocardiographic pattern in certain individuals has been convincingly demonstrated.

Various factors, chemical, mechanical and nervous, contributing to the development of transient bundle branch block, have been suggested, and attention has been repeatedly called to the influence of indirect vagal effects.<sup>6, 7, 8, 17, and 18</sup> Although experimentally stimulation of the vagus has been shown to affect intraventricular conduction,<sup>19</sup> clinical evidence of this is not clear and in those cases in which vagal influence is suggested it seems impossible to determine just what may represent a direct effect or manifest an indirect response to other vagal actions, principally slowing of the heart rate. Until the Wolff-Parkinson-White syndrome is completely understood the action of atropine in those instances in which the conduction mechanism is affected by the drug will remain in doubt. Recent histological studies have raised again a question in the minds of certain investigators as to the existence of a sufficiently distinct anatomical structure in the human heart to warrant the name of a bundle branch system.<sup>20</sup> In view of conflicting studies and opinions on this point in the accumulated literature of the past it would seem reasonable to assume that the question was still open. Irrespective of the anatomical factors involved certain experimental evidence related to the effect of atropine on conduction in the intact mammalian heart appeared to throw some light on the apparent early vagal action of atropine on intraventricular conduction in the case presented here.

The effects of atropine on conduction in auricular, ventricular and A-V nodal tissue of the mammalian heart under very high rates of stimulation have been studied at length.<sup>21</sup> Under these conditions, when doses of atropine sufficient to paralyze the vagus are given, the refractory period in all three types of tissue is prolonged leading to varying degrees of block. The refractory period of A-V nodal tissue is similarly influenced by section of both vagi. Conversely it

has been demonstrated in the case of auricular muscle under very high rates of stimulation that increased vagal tone decreases the refractory period.<sup>22</sup> In general, however, the effect of vagal stimulation on the A-V node is to prolong conduction time through the node and produce varying degrees of A-V block. It has been pointed out that any concept of the action of the vagus on the heart must explain these apparently paradoxical effects and an hypothesis based on a dual action of the vagus has been suggested.<sup>23</sup> According to this concept vagal stimulation not only shortens the refractory period but also decreases the rate at which excitability returns, and this latter effect on the A-V node which has a longer refractory period and presumably slower metabolic processes is more marked and the determining vagal influence on conduction through the A-V node. In applying this concept to the interpretation of certain experimental results where vagal stimulation has decreased the degree of A-V block it has been suggested that under certain conditions the generally negligible effect on the refractory period becomes the one of primary influence.<sup>23</sup> Instances in which vagal stimulation clinically have shortened rather than prolonged A-V conduction have been reported.<sup>23</sup> It does not seem unreasonable to assume that a similar state of affairs may exist in the conduction pathways from the node to the ventricles and that conduction along these pathways is subject to similar influences.

In this case the early parasympathomimetic effect of atropine did not affect the P-R interval but was associated with periods of transient normal intra-ventricular conduction. One is led to consider the possibility of vagal action on the conduction mechanism other than a decrease in heart rate and immediately related effects, and that this reversion to normal conduction might result from a transient decrease in the refractory period of the abnormally functioning part of the conduction pathway leading to the right ventricle.

### SUMMARY

A case of right bundle branch block with a wide S-wave pattern occurring in a 28 year old soldier without other evidence of heart disease is presented. Transient periods of normal conduction were observed to occur once spontaneously, once during stimulation of the left carotid sinus and on three occasions during the early period of parasympathomimetic action following the subcutaneous injection of 1.5 mg. of atropine. The phenomenon is briefly discussed.

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## MEDIASTINAL EMPHYSEMA FOLLOWING ANTERIOR PERFORATION OF A GASTRIC ULCER\*

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DURING the past 20 years mediastinal emphysema has been recognized with increasing frequency and a large number of papers are now available in the medi-

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cal literature bearing on its pathologic physiology and clinical manifestations.<sup>1, 2, 3, 4, 5</sup> McGuire and Bean<sup>6</sup> have credited Laennec with the original description of the peculiar bubbling, crackling and popping sounds now considered so characteristic. Müller,<sup>7</sup> in 1888, described bubbling crepitations synchronous with the heart beat as indicative of pneumomediastinum.

Mediastinal emphysema is most often a complication of another disease or condition. Air can reach the mediastinum from perforation of the esophagus, trachea or bronchus. It may extend to the mediastinum from a collection of air introduced into the fascial planes of the neck or from a collection of air in the retroperitoneum. For years it was assumed that air frequently entered the mediastinum from a ruptured emphysematous bleb, although this rarely if ever has been confirmed at post mortem. Macklin,<sup>8, 9</sup> in a series of experiments on cats and other animals, has clarified the mechanism of what is probably the most common cause of mediastinal emphysema, namely interstitial emphysema of the lungs. He has been able to show that under increased intra-pulmonary pressure the air may enter the perivascular sheaths of the finer branches of the pulmonary vessels and move along these sheaths toward the root of the lung. Some of this air may go peripherally but apparently most of it collects in the hilar region as a result of pressure gradients and finally bursts through into the mediastinum. This sequence of events is more likely to occur when partial bronchial obstruction exists to produce distention and easier rupture of alveoli. Alveolar rupture is thought to be truly spontaneous at times when no definite condition tending to increase intra-alveolar pressure is found. Hamman,<sup>10, 11, 12</sup> more than any other, has directed our attention to this condition and correlated our knowledge in a comprehensive manner.

The purpose of this communication is to present an instance of mediastinal emphysema apparently arising secondary to pneumoperitoneum following perforation of a gastric ulcer. The mediastinal emphysema was a confusing aspect of the clinical picture.

#### CASE REPORT

H. B., a 58 year old single man, a laborer and plasterer by occupation, was admitted to the United States Veterans Hospital at Hot Springs, South Dakota for the fifth time on September 5, 1945. The admissions over a four year period had been for treatment of carcinoma of the tongue with extension into the mandible. This tumor had been treated first with radium and then by excision of the anterior two-thirds of his tongue in August 1942. In his last admission it was not certain whether he had a local extension of malignancy into the mandible or whether the bone was involved in irradiation necrosis. Roentgenogram of the chest showed no metastasis and very slight increase in the broncho-vascular markings. The patient had no gastrointestinal complaints until just after the evening meal on January 9, 1946 when he developed quite suddenly a severe steady upper abdominal pain. When seen in medical consultation the following morning examination disclosed temperature 103.8° (rectally), pulse 116, respirations 28, blood pressure 90 mm. Hg systolic and 60 mm. diastolic. The patient was an elderly man appearing acutely ill, cyanotic and apprehensive with upper abdominal and lower anterior chest pain. There was no icterus of skin or sclera. The stump of the tongue and the pharynx appeared dry. A small ulceration was present on the inner aspect of the left mandible. The left anterior cervical nodes were marble-sized and quite firm. The trachea was in the mid-line. The thyroid gland was not palpable. The neck veins were moderately distended with

patient in the semi-recumbent position. There was no evidence of subcutaneous emphysema. The anterior-posterior diameter of the chest was slightly increased and the subcostal angle obtuse but otherwise the lungs were clear. The heart borders could not be outlined and the point of maximal impulse could not be seen or felt. A peculiar grating sensation was palpable over the precordium at the level of the third, fourth and fifth interspaces to the left of the sternum. On auscultation over the precordium the cardiac tones were obscured by loud crackling, crunching and popping sounds accentuated by deep inspiration. The sounds continued, however, even in absence of respiration and were alternately louder and fainter depending on the phase of the cardiac cycle. The upper abdomen was markedly rigid and tender on pressure. The liver, spleen and kidneys could not be felt. There were no masses or herniae. The lateral lobes of the prostate gland showed moderate firm enlargement, otherwise the rectal examination was negative. The white blood cell count was 26,850 with 96 per cent polymorphonuclears and 4 per cent lymphocytes; red blood cells 5,600,000; hemoglobin 90 per cent. The urine was within normal limits. Wassermann and Kahn reactions were negative.

The question immediately arose as to whether acute mediastinal emphysema could explain all of his symptoms or whether the mediastinal emphysema was secondary to a perforated abdominal viscus. Because of the critical condition of the patient it was difficult to carry out adequate roentgenologic examinations. Portable anterior posterior roentgen-ray of chest showed a high left diaphragm but no definite air in the mediastinum. A satisfactory lateral roentgen-ray of the chest could not be obtained. With the patient tilted at a 45 degree angle a large amount of air was visualized under the dome of the diaphragm. Laparotomy was done and a perforated ulcer was found on the anterior-superior aspect of the lesser curvature of the stomach about two inches above the pylorus. Very little scar tissue was found about the ulcer. Apparently it was an acutely ulcerative process. The ulcer was closed and postoperatively the patient did surprisingly well. The bubbling, crackling and popping sounds gradually diminished in intensity until they disappeared altogether on the fourth post-operative day. The heart sounds then were heard normally, were regular, of good quality and without murmurs. Three weeks later when the patient had apparently completely recovered from the acute episode he had a sudden massive hemorrhage from the left mandible and died as a result of this. Postmortem examination was denied us.

### DISCUSSION

It is not clear how air can reach the mediastinum from a collection of intra-peritoneal air when the parietal peritoneum has not been injured. Both the lesser and greater peritoneal cavities are closed spaces. It is easy to see how air in the retroperitoneum can gain access to the mediastinum through the aortic, esophageal or vena caval hiatuses or conversely how mediastinal air can extend to produce pneumo-retroperitoneum as in Adcock's case.<sup>13</sup> Perforation of the stomach high in the cardia in the area not covered with peritoneum or perforation of an ulcer on the posterior wall of the duodenum can lead to mediastinal emphysema without first producing pneumoperitoneum. A number of such cases have been reported.<sup>14, 15, 16</sup>

Banyai and Jurgens<sup>17</sup> report seven cases of mediastinal emphysema following artificial pneumoperitoneum. It is significant, however, that in all of these cases the pneumoperitoneum was induced by the subphrenic route. In this method the point of the needle is supposed to be above the costal margin and below the costophrenic reflection of pleura. It would thus be possible for the needle to traumatize the diaphragm, to elevate the basal parietal pleura or to penetrate the lung it-

self. Thus the air could gain access to the mediastinum without having first to traverse the peritoneal cavity. McCorkle and Stevenson<sup>18</sup> report a case in 1937 of perforation of an ulcer on the anterior surface of the duodenum with pneumoperitoneum, mediastinal emphysema and subcutaneous emphysema. In their case no abnormal cardiac signs are mentioned and the anterior-posterior chest roentgenogram reveals no evidence of air in the mediastinum. The authors specifically mention that there was no evidence of posterior perforation of the duodenum.

Two ways in which gas might extend from the peritoneal cavity to the mediastinum to the subcutaneous tissues have been suggested<sup>14, 15</sup>: 1. By direct diffusion through the parietal peritoneum especially when the pneumoperitoneum is extensive and under pressure and when the parietal peritoneum is damaged by inflammatory process. 2. Diffusion of gas from the site of perforation subserously along peritoneally covered ligamentous structures such as the hepato-duodenal or round ligament to the umbilicus or by way of the phrenico-esophageal ligament and aortic hiatus into the mediastinum.

Experimentally in cadavers and dogs Podlaha<sup>16</sup> demonstrated the pathways of extension of gas from the various parts of the stomach and duodenal regions. He injected hydrogen peroxide into the subserous tissues and found that, from injection around the pylorus, the material passed along the hepato-duodenal and round ligament to the umbilical region and that, from injection around the cardia, the material principally followed the phrenico-esophageal ligament and aortic hiatus into the posterior mediastinum.

In view of Macklin's work showing how gas can follow the vascular sheaths of blood vessels a third way is suggested. A subperitoneal collection of gas could enter the perivascular sheaths of the great vessels supplying the region of the perforation and extend eventually to reach the aorta and pass through the aortic hiatus into the mediastinum.

The objection may be raised in my case that the mediastinal emphysema was merely a coincidence and might have been secondary to the carcinoma about the mandible or possibly have had a direct pulmonary cause. Unfortunately no autopsy was obtained to eliminate these possibilities. However, there was no emphysema about the tissues of the neck at any time and this might have been expected were the gas extending from the mandibular region. Its appearance at the time of or shortly after the ulcer perforation and its rapid disappearance following closure of the perforation lead me to feel that the perforation was more than a coincidental event. There was no definite evidence of pulmonary disease.

### SUMMARY

Mediastinal emphysema can occur following perforation of a peptic ulcer into the peritoneal cavity. A case is reported and the available literature briefly reviewed. Theoretically the gas could extend to the mediastinum by (a) passage along the perivascular sheaths of the great vessels to the aorta and through the aortic hiatus into the mediastinum, (b) direct diffusion through the parietal peritoneum, (c) passage along the phrenico-esophageal ligament and through the aortic hiatus when the perforation is near the cardia. It is felt most likely that the gas followed the perivascular sheaths of the great blood vessels to reach the mediastinum in this case.

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## DISSEMINATED LUPUS ERYTHEMATOSUS WITH PERICARDIAL EFFUSION \*

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DISSEMINATED lupus erythematosus, although not a common disease, is more frequently recognized than in the past, and as more and more observations are

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recorded, it becomes apparent that it represents a syndrome in which there may be varying visceral and cutaneous manifestations. It is essentially a diffuse vascular disease involving the small vessels of the skin and viscera, although recent studies<sup>1</sup> in which fibrinoid degeneration and sclerosis of the collagen are described as the fundamental change in lupus erythematosus indicate that the concept of a diffuse disease of the peripheral circulation can no longer be entertained without question.

Hebra,<sup>2</sup> in 1845, first described lupus erythematosus under the name "seborrhea congestive." Six years later Cazenave<sup>3</sup> gave the disease its present name, but it was not until 1872 that Kaposi<sup>4</sup> subdivided the disease into "lupus erythematosus discoides" and "lupus erythematosus discoides and aggregatus" and pointed out the systemic manifestations of the latter form. Although this early investigator described the clinical picture much as we know it today, several articles published since that time stand out as being particularly valuable in determining the many and varied manifestations of this confusing syndrome. These observations include the erythema group of cutaneous diseases with visceral manifestations described by Sir William Osler in 1895, 1900, and 1904,<sup>5,6,7</sup> the atypical verrucous endocarditis recognized by Libman in 1911, and reported more fully by Libman and Sachs in 1924,<sup>8</sup> the polyserositis, polyarthritis and glomerulonephritis with long-continued fever described by Christian in 1935,<sup>9</sup> and a diffuse disease of the peripheral circulation usually associated with lupus erythematosus and endocarditis described by Baelhr and associates the same year.<sup>10</sup> The Reifenssteins<sup>11</sup> have emphasized the relationship between these manifestations; and the work of Montgomery<sup>12</sup> and Klemperer, et al.<sup>1</sup> has contributed greatly to a better understanding of the fundamental pathological process.

However, despite the varying and often confusing lesions reported in this disease, we have been unable to find a reported case in which a pericardial effusion was the most striking and troublesome manifestation, nor one accompanied by an adhesive pericarditis. Jarcho<sup>13</sup> reports a case in which there was a sacculated pericardial effusion; Fox<sup>14</sup> described a patient in whom a terminal pericardial effusion, 500 c.c., was found at autopsy, and Contratto and Levine's case<sup>15</sup> had 250 c.c. of fluid at postmortem examination, but no previous clinical or roentgenological evidence of pericardial effusion. A patient reported by Blount and Barrett<sup>16</sup> had 100 c.c. of light yellow fluid in the pericardium at autopsy, but the only clinical evidence was an electrocardiogram compatible with such a diagnosis. Numerous authors report that "pericarditis" (without a qualifying diagnosis) is common, but do not mention pericardial effusion per se, whereas Rose and Goldberg<sup>17</sup> state that pericarditis with effusion has been described in detail by various writers, but do not give references. Rakov and Taylor<sup>18</sup> on the other hand, point out that pericarditis with effusion is a rare manifestation of disseminated lupus erythematosus and there are reports of numerous cases<sup>1,5,6,11,13,14,15,16,17,19,20,21,22,23</sup> in which there is no recorded evidence of a clinical diagnosis of pericardial effusion. Although disseminated lupus erythematosus has been observed by the authors many times, the patients reported here are the only ones in which a pericardial effusion has been recognized clinically.

#### CASE REPORTS

*Case 1.* A 23 year old white single female was first admitted to the University Hospital on July 19, 1942, complaining of dyspnea and vomiting. Generalized malaise



and tiredness had been present for 18 months. In February 1942, she developed a migratory polyarthrititis with swelling, pain, redness, increased heat and pain on motion in the joints of the wrist, ankles, knees, elbows, shoulders, fingers and toes. She was feverish at the time, but did not consult a physician. After a period of two to three weeks the symptoms subsided spontaneously without residue, only to recur several times during the interval between the onset of her acute symptoms and her admission to the hospital. Since the onset of the joint symptoms she had noted shortness of breath on exertion and one month prior to admission had an attack of paroxysmal nocturnal dyspnea. She had had a daily elevation of temperature as high as 104° F. for four weeks prior to admission. She had lost eight pounds in weight during the illness and had vomited several times the day before admission to the hospital.

*Physical Examination:* The patient was an acutely ill, well developed and nourished white female. Temperature 103° F., pulse 100, respirations 24, blood pressure 118 mm. Hg systolic and 74 mm. diastolic. There were no skin lesions. The neck veins were slightly engorged. The lungs were clear. There was enlargement of the heart; the point of maximum impulse could not be felt. There was a gallop rhythm and a friction rub was heard just to the left of the sternum in the third and fourth interspaces. There was a paradoxical pulse of 30 mm. of mercury. The liver was palpable four fingers below the right costal margin. The joints were not abnormal, and the remainder of the physical examination was essentially negative.

*Laboratory Findings:* The hemoglobin varied from 43 to 70 per cent, the red blood count from 2,200,000 to 4,800,000 per cu. mm., and the white blood count from 5300 to 18,800 per cu. mm. The differential count was essentially normal except for a slight increase in polymorphonuclear cells. Repeated urinalysis revealed a one to two plus albumin, one to two white blood cells, none to two red blood cells and an occasional hyaline cast. Sedimentation rate was 0.73 mm. per minute. Urea clearance was 111 per cent in the first hour and 59 per cent in the second hour. Routine serological test for syphilis was positive. However, verification tests and additional studies revealed this to be a false positive reaction. A roentgen-ray examination of the chest revealed an enlarged heart and pericardial effusion (figure 1). The electrocardiogram was interpreted as being consistent with the diagnosis of pericarditis.

*Course in Hospital:* Treatment consisted of complete bed rest, ferrous sulfate, vitamin supplements and salicylates. A few days after admission the patient developed a recurrence of her arthritis, and this as well as the fever subsided after the use of large amounts of salicylates. The pericardial effusion subsided gradually, and the venous pressure returned to normal. During this hospitalization she had a rash which was diagnosed as a contact dermatitis from the bleach used in the bed linen. She was discharged September 17, 1942, with a diagnosis of rheumatic fever and advised to continue the regimen that had been followed in the hospital and to return in three months.

She was re-admitted December 16, 1942. During her stay at home she had continued to have recurrences of the arthritis and fever, and one week prior to admission she developed a recurrence of the dyspnea. Physical examination at this time was essentially the same as that of the first admission except that no friction rub was heard. Treatment was the same as on the previous hospitalization, and the diagnosis of rheumatic fever was reaffirmed. Approximately one month after admission she developed erythema on the nose and malar eminences and subsequently a typical eruption of disseminated lupus erythematosus. Laboratory studies during this admission were as follows: Hemoglobin 75 per cent, red blood count 4,100,000 per cu. mm., white blood count 3100 to 7700 per cu. mm., urinalysis showed a three plus albumin, 5 to 10 white blood cells, 30 to 40 red blood cells, and hyaline and granular casts; urea clearance was 69 per cent in the first hour and 36 per cent in the second. Total serum proteins 9.0 gm. per 100 c.c. with the albumin being 2.1 and the globulin 6.9, making

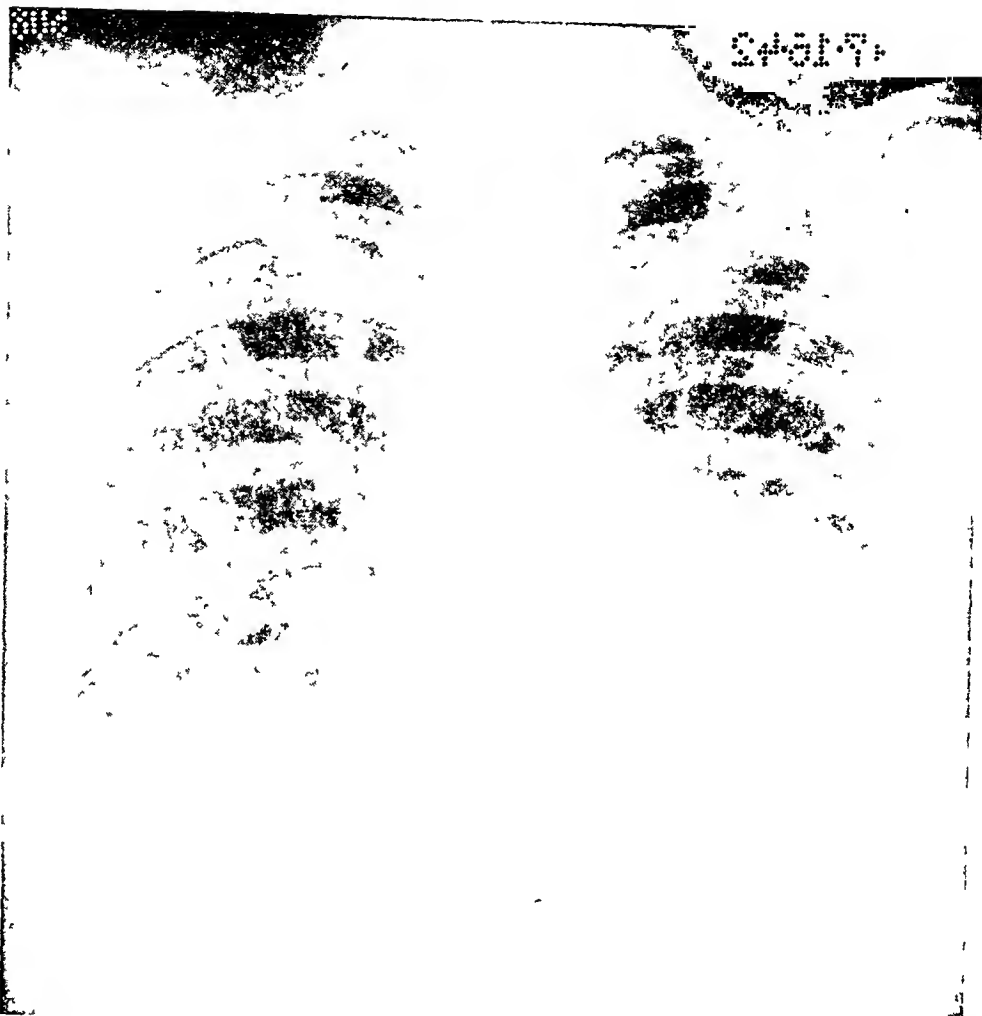


FIG. 1. A roentgen-ray of the chest of Case 1 taken July 16, 1942. There is marked enlargement of the cardiac shadow, and the configuration is globular. There is no prominence of pulmonary vascular markings as one would expect in the presence of marked mitral stenosis with pulmonary congestion, and there is no evidence of any active pulmonary disease. The appearance of the silhouette is that of pericardial effusion.

a ratio of 0.3. The electrocardiogram and the roentgenogram of the chest were essentially the same as on the first admission. After the diagnosis of lupus erythematosus became apparent, treatment with testosterone, 25 mg every other day, was begun, and on March 22, 1943, she had a radium implant for sterilization. In spite of the above treatment and general supportive measures, the pericardial effusion became more marked, and she developed pneumonia, pleural effusion, gallop rhythm, evidence of increasingly impaired renal function, and on April 7, 1943, she had a convulsion and died. Permission for autopsy was not granted.

*Case 2.* A 25 year old white married female was first admitted to University Hospital, May 16, 1946. One and a half years prior to admission she had developed numbness, pain and color changes in the tips of the fingers and toes upon exposure to cold. This recurred many times and was relieved only by heat. She was advised to go to Florida in 1945, and while there developed a dry gangrene of the tip of the right index finger which healed without difficulty. During her stay in Florida, she developed mild swelling of the ankles, wrists and proximal interphalangeal joints. She returned to her home in Michigan in 1946, and shortly afterward developed

two penny-sized erythematous lesions on either side of the nose. The eruption gradually spread to involve the malar areas, and she developed fever, malaise, generalized aching and occasional sharp, intermittent pains just to the right of the sternum. She was admitted on the neuro-surgical service to have a sympathectomy, the admitting diagnosis being Raynaud's disease and scleroderma. The diagnosis of disseminated lupus erythematosus was made by the sudden appearance of characteristic facial erythema and she was promptly transferred to the Dermatology service.

*Physical Examination:* Temperature 100° F., pulse 96, respirations 22, blood pressure 120/76. The patient was well developed, nourished and appeared acutely ill. There was an erythematous lesion involving the nose, chin and flush area of the face. An erythema of the volar surface of the tips of several fingers and swelling of the proximal interphalangeal joints of the middle and ring fingers of both hands were present. There was tenderness of the calf muscles and ankles. The remainder of the physical examination was essentially negative.

*Summary of Laboratory Findings:* All urine specimens taken during this hospitalization showed a two to three plus albumin, a few red cells, a few white cells, and a few granular casts. Her blood picture showed a mild secondary anemia and a



FIG. 2. A roentgen-ray of the chest of Case 2 taken May 17, 1946, during an acute exacerbation of her lupus erythematosus, but before the pericardial effusion occurred. The lung fields are clear, and the cardiac shadow is of normal size and configuration

normal white blood cell count and differential count. Urea clearance showed 147 per cent excretion in the first hour and 70 per cent in the second. The nonprotein nitrogen was 36.2 mg. per cent. Roentgen-ray examination of the chest on admission was essentially negative (figure 2), but subsequent examinations revealed the development of cardiac enlargement, pericardial effusion (figure 3), pulmonary congestion and pleural effusions (figure 4). Examinations of the gastrointestinal tract by means of a barium meal demonstrated no abnormality. Biopsy of the gastrocnemius muscle was essentially normal.



FIG. 3. A roentgen-ray of the chest of Case 2 taken August 8, 1946. There is marked globular enlargement of the cardiac shadow, and its appearance is entirely compatible with a diagnosis of pericardial effusion.

*Course in the Hospital:* Treatment consisted of multiple small blood transfusions and Lugol's solution by mouth. Shortly after admission the patient showed temporary improvement with a lowering of her temperature, pulse and respirations. Subsequently, however, she developed pneumonia and cardiac failure, the former responding to penicillin and an oxygen tent and the latter to digitalization and a diuretic regimen. From time to time she had erosions on the hard palate, buttocks and shoulders. At the time of discharge on June 28, 1946, she was somewhat improved, but continued to show an enlarged heart and pericardial fluid.

The patient was readmitted to the Hospital on July 28, 1946. One week after her return home she began to develop ankle edema, epigastric discomfort, dysphagia,



FIG. 4. A roentgen-ray of the chest of Case 2 taken August 16, 1946. There is a massive pericardial effusion as well as a left pleural effusion. Tamponade, but not myocardial failure, was present. There are suggestive signs of increased density of the parenchyma of the left lung, but the field is almost completely obscured by fluid. The right lung remains clear.

vomiting, and daily temperature elevations of 100° to 101° F. Physical examination at the time of admission revealed a chronically ill white female who was moderately dyspneic and was most comfortable when sitting up. Her temperature was 101° F., pulse 100, respirations 28 and blood pressure 106/70. There were sclerodermatous changes of the skin of the hands, wrists and arms. The face was quite clear. A small erosion was present on the hard palate. The right lung was entirely clear; there were signs of fluid at the left base. The area of cardiac dullness was enlarged to the mid-axillary line on the left and 3 cm. to the right of the sternum on the right. The sounds were faint, the rhythm regular and there were no murmurs. There was moderate distention of the abdomen with gas, and the liver edge was palpable. A moderate edema was present over the ankles and the sacrum, and minimal swelling and pain on motion of the proximal interphalangeal joints of the middle and ring fingers of both hands. The wrists were only slightly painful on motion, and there was limitation of motion of the left temporomandibular joint.

*Summary of Laboratory Findings:* Urinalysis on admission showed a one plus albumin, an occasional red cell, an occasional white cell, and one to two casts per high power field. The specific gravity was 1.012. Throughout the hospital stay, the urine continued to show a two or three plus albumin. The red cells and casts disappeared,

but the white cells increased until there were 10 to 15 per high power field. The specific gravity of the urine was never higher than 1.013. A routine blood examination on admission showed 86 per cent hemoglobin with 4,000,000 red blood cells per cu. mm. The white blood count was slightly elevated, 13,650 per cu. mm., with a normal differential.

An electrocardiogram taken on admission showed a P-R interval of 0.28, QRS 0.07. There were small deflections in all leads, inverted T-wave in Leads I and II and chest Leads V and VI inclusive. Total serum protein shortly after admission was 8.1 per cent, albumin 3.6 per cent and globulin 4.5 per cent. Blood nonprotein nitrogen on September 17 was 35.4 mg. per cent. Blood chloride on September 19 was 533 mg. per cent. Total serum protein on September 19 was 5.6 per cent, albumin 1.9 per cent and globulin 3.7. Roentgen-ray examinations of the chest during this admission again showed cardiac enlargement and pericardial and pleural effusions, and were taken serially during this hospitalization in order to follow the status of the effusion.

*Summary of Course in the Hospital:* On admission the patient was started on a diuretic regimen and showed considerable weight loss but no decrease in the amount of pericardial fluid. On August 10, the first pericardial tap was done with the removal of 420 c.c. of clear pale yellow fluid which was a typical transudate. Following this she required a pericardial tap at intervals of approximately one week, some being necessitated by acute cardiac tamponade. From 510 c.c. to 910 c.c. were removed each time. On three occasions it became necessary to do a pleural thoracentesis, approximately one liter being removed each time. Her course was gradually downward, and she required large amounts of narcotics for relief of chest pain and headaches. General supportive and symptomatic treatment were of no avail. Because of severe nostalgia and adequate facilities for home care, the patient was discharged September 22, 1946. Information received from the patient's family was that her course continued to be downward with the development of convulsive seizures and death approximately one month after discharge. No autopsy was obtained.

## DISCUSSION

The cutaneous and visceral manifestations as well as the pathological process in disseminated lupus erythematosus have been fully discussed in numerous other reports and no attempt is made to cover the disease in detail. However, the occurrence of pericardial effusion, together with ascites and pleural effusion, in this syndrome has not been clearly delineated in the past, and a review of the literature would lead one to believe that it is unusual as a clinical manifestation. The experience in this Clinic corroborates that impression, but we have seen two cases in which it presented a major problem, one case requiring five pericardial taps, and its presence in another leading to the erroneous diagnosis of rheumatic fever until the development of cutaneous lesions made the diagnosis apparent. Certainly lupus erythematosus is a disease to be considered in the differential diagnosis of pericardial effusion, especially when this finding is associated with other more common manifestations of the disorder.

## SUMMARY

Two cases of disseminated lupus erythematosus are reported. Pericarditis and the presence of small amounts of pericardial fluid at autopsy have been relatively common, but massive effusions presenting a major therapeutic problem such as occurred in one of our patients (case 2) have not been previously re-

ported. In our other patient a pericardial effusion was responsible for many of her symptoms and signs.

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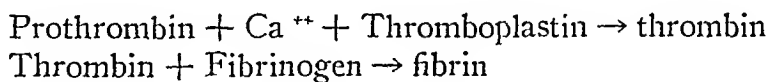
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## EDITORIAL

### RECENT STUDIES IN PROBLEMS OF BLOOD COAGULATION

INTEREST in the problems of blood coagulation stems not only from recent studies of those disturbances which lead to hemorrhagic manifestations, but also from those variations in the mechanism which may be responsible for hypercoagulability. The clinical use, in thromboembolic diseases, of agents, such as heparin and dicumarol, which modify the coagulability of blood has steadily increased. A rational approach to the management of spontaneous or induced disorders of the hemostatic mechanism demands consideration of concepts revised by the accumulation of new and important experimental data. The clinician attempting such a survey will be hampered to some extent by a terminology completely intelligible, perhaps, only to the select group known as "coagulationists." In some instances variations in nomenclature were undoubtedly accentuated by a war-imposed scientific hiatus between this country and some parts of Europe. This is particularly true in regard to important studies emanating from the Scandinavian countries. An effort will be made to touch briefly upon selected phases of this large problem.

Proper orientation requires a fixed point of departure. In spite of numerous other proposals there seems to be general agreement that the classical Morawitz theory of blood coagulation offers the best framework upon which new concepts can be superimposed. It will be recalled that according to this theory, coagulation takes place in two stages as illustrated by the well known formula—



Jacques<sup>1</sup> observes that hemostasis represents a summation of at least three factors—formation of the fibrin clot, platelet adhesion, and the vascular response—which do not necessarily operate together in all instances of abnormal bleeding. A breakdown of one factor can exist without complete disruption of the hemostatic mechanism. This is exemplified by the recent observation of a number of instances of complete, apparently congenital, afibrinogenemia<sup>2</sup> in which the total inability to form a clot was associated with hemorrhagic manifestations no more severe than with mild hemophilia. Simultaneous disturbance of several aspects of the hemostatic mechanism will on the other hand usually produce a serious bleeding tendency.

Initiation of the clotting reaction requires the activity of a thromboplastic mechanism for transformation of prothrombin to thrombin. Studies of the

<sup>1</sup> JACQUES, L. B.: Blood clotting and hemostasis, in *Blood Clotting and Allied Problems*, The Josiah Macy Jr. Foundation, New York, N. Y., p. 9.

<sup>2</sup> MACFARLANE, R. G.: A boy with no fibrinogen, *Lancet*, 1938, i, 309.



coagulation defect in hemophilia disclosed that a plasma constituent was essential in this phase of the reaction.<sup>3</sup> This substance, globulin in nature, is apparently absent from the blood of hemophiliacs. Plasma fractionation technics developed by Cohn et al. have localized this anti-hemophilic globulin to so-called Fraction I.<sup>4</sup> Prior to the discovery of this factor all thromboplastic activity was considered to reside within the platelets. Focussing of attention upon "plasma thromboplastin" led to the assignment of the platelets to a relatively minor rôle in thrombin formation. It is now recognized, although the exact relationship is not clear, that both elements are essential for thromboplastic action. In 1946, Jacques et al.<sup>5</sup> introduced the technic of coating syringes, needles and glassware with silicone. Blood collected in this manner will remain fluid for several hours, apparently due to preservation of the platelets. By prolonged centrifugation in the cold in silicone coated tubes Brinkhous<sup>6</sup> has been able to completely remove platelets and produce an incoagulable plasma. The addition of such plasma to similarly treated hemophilic plasma did not correct the coagulation defect. On the other hand, the addition of such plasma to whole hemophilic blood containing platelets did correct the coagulation delay. Both platelets and plasma factor are essential for normal thromboplastic activity. Quick<sup>7</sup> has attempted to incorporate the plasma factor in the classical coagulation reaction by assigning to it the term, thromboplastinogen, to indicate its existence in an inactive state in the plasma. Vascular injury, resulting in the breakdown of platelets, liberates from them an enzyme which transforms thromboplastinogen to thromboplastin and thus permits the coagulation mechanism to proceed.

It seems clearly established that plasma contains a proteolytic enzyme, in an inactive state, which because of its characteristic behavior has been termed fibrinolysin (plasmin).<sup>8</sup> The inactive state is referred to as profibrinolysin (plasminogen). It is this enzyme which is transformed from an inactive to an active phase by an enzyme liberated by streptococci, known as streptokinase. The exact position of fibrinolysin in the coagulation reaction is not too clearly understood at this time. Ferguson<sup>9</sup> has attempted to assign to a plasma proteolytic enzyme, presumably identical with fibrinolysin, a major rôle in the initiation of clotting. According to this investigator

<sup>3</sup> PATCH, A. J., JR., and STETSON, R. P.: Hemophilia. II. Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of hemophilic blood, *Jr. Clin. Invest.*, 1937, xvi, 113.

<sup>4</sup> MINOR, G. R., DAVIDSON, C. S., LEWIS, J. H., FAGNON, H. J., and TAYLOR, F. H. L.: The effect in hemophilia of the parenteral administration of a fraction of the plasma globulins rich in fibrinogen, *Jr. Clin. Invest.*, 1945, xxiv, 704.

<sup>5</sup> JACQUES, L. B., FIDLAR, E., FELDSTED, E. T., and MACDONALD, A. G.: Silicones and blood coagulation, *Canad. Med. Assoc. Jr.*, 1946, lv, 26.

<sup>6</sup> BRINKHOUS, K. M.: Initiation and acceleration factors in thrombosis, in *Blood Clotting and Allied Problems*, The Josiah Macy Jr. Foundation, New York, p. 39.

<sup>7</sup> QUICK, A. J.: Studies on the enigma of the hemostatic dysfunction of hemophilia, *Am. Jr. Med. Sci.*, 1947, ccxiv, 272.

<sup>8</sup> MACFARLANE, R. G., and BIGGS, R.: Fibrinolysis, its mechanism and significance, *Blood*, 1948, iii, 1167.

<sup>9</sup> FERGUSON, J. H.: Mechanism of blood coagulation, *Am. Jr. Med.*, 1947, iii, 67.

plasma tryptogen (profibrinolysin?) is activated to tryptase (fibrinolysin?) by the colloidal disturbance produced by vascular damage. The proteolytic enzyme then behaves as a thromboplastic agent. This view has not been substantiated as yet.

A major advance in the study of problems of blood coagulation occurred with the introduction in 1935 of the Quick<sup>10</sup> method of determining prothrombin clotting time. In this procedure the addition of an excess of tissue thromboplastin and an optimal amount of calcium to oxalated plasma resulted in the rapid formation of thrombin with resultant fibrin formation and clotting. The speed of the reaction was said to depend entirely upon the concentration of prothrombin present which thus constituted the chief variable. It is not our purpose, at this time, to enter into the merits of this procedure. However, it is germane to the discussion to call attention to the recently demonstrated fact that the formation of thrombin depends not only upon the concentration of prothrombin but also upon an additional substance present in the globulin fraction of plasma which has been independently reported by several investigators. Owren refers to this material as Factor V<sup>11</sup> while Seegers<sup>12</sup> terms it AC (accelerator) globulin. A deficiency of this substance will produce delay in the formation of thrombin and thereby create a false impression concerning the concentration of plasma prothrombin. The clinical significance of this factor remains to be determined by further study. Owren has recently reported a case characterized by a hemorrhagic tendency which was associated with both a prolonged prothrombin time as well as a prolonged clotting time. In this case a deficiency of Factor V was present. The entity has already been referred to as "Owren's disease" or "parahemophilia." It is possible that previously reported instances of so-called idiopathic hypoprothrombinemia were, in reality, this entity. Recent studies by Seegers et al.<sup>13</sup> indicate that AC-globulin is formed in the liver and like other blood clotting factors is reduced in liver disease. Ferguson and Lewis<sup>14</sup> point out that AC-globulin is not identical with antihemophilic globulin. Ware and Seegers<sup>15</sup> suggest that AC-globulin exists in an inactive state as plasma accelerator globulin which is transformed by the initial amounts of thrombin formed in the first stage of the clotting reaction to serum accelerator globulin. The latter in turn

<sup>10</sup> QUICK, A. J., STANLEY-BROWN, M., and BANCROFT, F. W.: A study of the coagulation defect in hemophilia and in jaundice, *Am. Jr. Med. Sci.*, 1935, cxc, 501.

<sup>11</sup> OWREN, P. A.: The coagulation of blood, *J. Chr. Gunderson, Oslo*, 1947, 100.

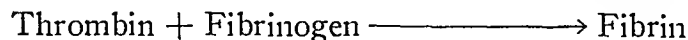
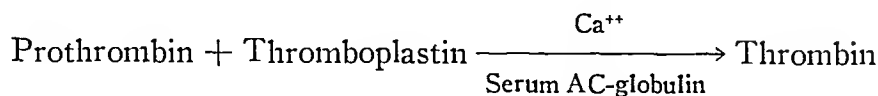
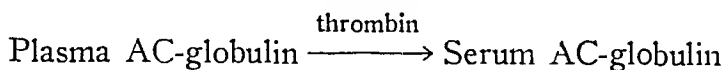
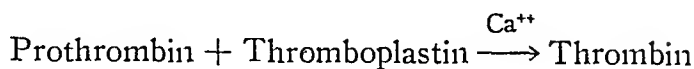
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<sup>14</sup> FERGUSON, J. H., and LEWIS, J. H.: Accelerator globulin and antihemophilic globulin in thrombin formation from aged prothrombin and in hemophilic blood, *Proc. Soc. Exper. Biol. and Med.*, 1948, lxxvii, 228.

<sup>15</sup> WARE, A. G., and SEEGER, W. H.: Serum AC-globulin: formation from plasma AC-globulin: role in blood coagulation; partial purification; properties; and quantitative determination, *Am. Jr. Physiol.*, 1948, cliv, 567.

speeds up the first stage of the coagulation reaction. This concept may be represented schematically, as follows—



Concepts regarding the hemorrhagic diatheses must not only incorporate the material just presented, but also several additional disturbances recently described. Coagulation may be retarded by the presence of circulating anti-coagulants in the blood. Two varieties have been studied. Hemophiliacs treated by the repeated infusion of whole blood, plasma or anti-hemophilic globulin may develop, on an immune basis, an antibody against the plasma factor which they lack.<sup>16</sup> This antibody functions as an anticoagulant rendering the patient refractory to further transfusions and thus compounding his difficulties. The plasma of such patients when added to normal blood will interfere with coagulation. Allen and Jacobson<sup>17</sup> have recently described a bleeding tendency apparently associated with the presence of a heparin-like substance in the circulating blood. It has been shown that dogs exposed to whole-body irradiation develop a bleeding tendency not due solely to the associated thrombocytopenia, but to a circulating anti-coagulant resembling heparin. Treatment of these animals with anti-heparin agents such as protamine and toluidine blue resulted in return of the clotting time to normal in vivo and vitro. These workers,<sup>18</sup> in a preliminary report, noted transient improvement in the bleeding tendencies of four patients with acute leukemia and two with idiopathic thrombocytopenic purpura after the administration of toluidine blue. In an additional report from the same clinic<sup>19</sup> five patients who developed a hemorrhagic diathesis following treatment with nitrogen mustard were benefited by the use of anti-heparin materials. In all studies thrombocytopenia has been present, but evidence for an additional factor has been demonstrated. This line of investigation, although of considerable interest, must still be confirmed by additional studies before generalizations can be made.

<sup>16</sup> CRADDOCK, C. G., JR., and LAWRENCE, J. S.: Hemophilia: a report of the mechanism of the development and action of an anti-coagulant in two cases, *Blood*, 1947, ii, 55.

<sup>17</sup> ALLEN, J. G., and JACOBSON, L. O.: Hyperheparinemia: cause of the hemorrhagic syndrome associated with total body exposure to ionizing radiation, *Science*, 1947, cv, 388.

<sup>18</sup> ALLEN, J. G., BOGARDUS, G., JACOBSON, L. O., and SPURR, C. L.: Some observations on the bleeding tendency in thrombocytopenic purpura, *Ann. Int. Med.*, 1947, xxvii, 382.

<sup>19</sup> SMITH, T. R., JACOBSON, L. O., SPURR, C. L., ALLEN, J. G., and BLOCK, M. H.: A coagulation defect produced by nitrogen mustard, *Science*, 1948, cvii, 474.

The rational management of hemorrhagic disorders and the clinical use of anticoagulant therapy not only require detailed information of the various phases of the coagulation reactions, but also knowledge of some of the inadequacies of clinical testing of these reactions. This brief review of some of the more significant studies in this active field may serve to indicate that our former concepts of the blood coagulation process are constantly being expanded and modified and that recent gains in knowledge of new factors in this mechanism may have clinical applications.

M. S. S.

## REVIEWS

*Treatment of Rheumatism.* 4th edition. By W. S. C. COPEMAN, O.B.E., M.A., M.D., F.R.C.P. 258 pages; 14.5 × 22 cm. The Williams and Wilkins Company, Baltimore, Md. 1946. Price, \$4.00.

This book is written expressly for general practitioners. The author, a general physician, has endeavored to survey the whole field of rheumatism impartially, and to concentrate on practical therapeutic methods.

The first 108 pages consist of a series of chapters on rheumatic diseases: Acute rheumatic fever; chorea; non-articular rheumatism and fibrositis; sciatica; neuritis; gout; rheumatoid and osteo-arthritis, and spondylitis. Each chapter consists of a short clinical description and discussion of the disease in question, followed by a general outline of appropriate treatment. In the remaining 150 pages the author takes up a more detailed discussion of each form of treatment separately, describing technics and discussing their indications. Among the forms of therapy dealt with in this manner are drugs, diet, the eradication of focal sepsis, vaccines, physical methods including heat, massage, movement and exercise, manipulation, baths, colonic therapy, hormones, actinotherapy and orthopedics.

In a common sense way the author presents to the practitioner a summary of practical methods and indicates his own personal experience of each. He shows how easily many physical methods can be applied in the home, without expensive or cumbersome apparatus, but none the less effectively. He adopts the sane attitude towards osteopathy that we should not condemn what we do not understand; the osteopath makes calamitous mistakes through his ignorance of pathology, while we miss opportunities to help our patients by ignoring the undoubted successes of the osteopath. The author believes that the ability to perform simple manipulative measures should be part of the equipment of every practising physician. The final chapter is a brief one on prognosis.

The book is easy to read. The print is excellent and, although in places expression leaves much to be desired, it is written in lucid, conversational style. It is hard to accept all the author's claims and some of the reasons presented to explain the success of certain measures. But the book undoubtedly achieves its purpose, and leaves the reader with the salutary feeling that, even in its most chronic form, rheumatism is a far from dull and hopeless field. Much can be done to relieve, if not to cure, its victims.

H. L. M.

*Management of Common Gastro-Intestinal Diseases.* Edited by THOMAS A. JOHNSON. 280 pages; 16 × 24 cm. J. B. Lippincott Company, Philadelphia. 1948. Price, \$7.00.

This product of 22 authors is a small book in relatively large type. The 16 chapters present the more important, commoner gastrointestinal conditions.

A few are excellent, particularly those on the recognition of gastric malignancy, management of bleeding peptic ulcer, amebiasis, and enterogastrene. The chapters on pancreatic disease are stimulating but not particularly applicable to clinical practice.

Many chapters are fairly elementary in discussion and definition. A few authors seem to be battling for recognition. Some write in a controversial tone. However, on the whole the book furnishes a good review for clinicians with some knowledge

of the field. It is not to be unreservedly recommended to students nor as a guide to physicians without hospital facilities.

C. B. A.

*Cardiovascular Diseases.* By DAVID SCHERF, M.D., F.A.C.P., Assoc. Prof. Medicine, New York Medical College, and LINN J. BOYD, M.D., F.A.C.P., Prof. Medicine, New York Medical College. 478 pages; 18.5 × 26 cm. J. B. Lippincott Co., Philadelphia. 1947. Price, \$10.00.

A great deal of excellent material is concisely presented in this book and practically all aspects of cardiovascular diseases are covered. The sections on myocarditis and autonomic reflexes are especially worthwhile.

As one could readily judge from the number of pages, this is not an exhaustive text. The authors present their own views and cover the subjects with reasonable completeness, omitting detailed discussion on controversial points. The resulting brevity will be welcomed by medical students and physicians interested in reviewing cardiovascular diseases. Both groups will find the material easy to read and understand. For those specializing in cardiovascular diseases the book obviously would not serve as a comprehensive reference work.

To this reviewer the only major defect seems to be in the arrangement of subjects. Chapters follow each other without definite order, related subjects often being widely separated in the table of contents. This causes some lack of continuity in the text, which is not wholly compensated by the index and the rather full table of contents. For instance, there are 14 index references to the subject of shock, and yet, in none of these instances is this important subject covered very fully. It would seem that the book's value would be greatly enhanced by better organization.

E. E. L.

*Breast Feeding: A Guide to the Natural Feeding of Infants.* By F. CHARLOTTE NAISH. 151 pages; 13 × 19 cm. Oxford University Press, New York. 1948. Price, \$3.50.

This small book is basically an appeal for an increase in the frequency of the breast feeding of infants. The advantages of this natural method of feeding are stressed throughout. Frequent comparisons between the udder of the cow and the breasts of the mother are made and form the basis for pre- and post-natal breast care. The author advocates several questionable forms of therapy, such as the use of thyroid extract in the torporous infant to encourage the infant to take the offered feedings. The initial chapter, "The Mind of the Mother," is very well written and is highly recommended to all who deal with infant feeding.

J. E. B.

## BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Conditioned Reflexes and Neuron Organization.* By JERZY KONORSKI, Head of the Department of Neurophysiology in the Nencki Institute of Experimental Biology, etc. Translated from the Polish MS. under the author's supervision by STEPHEN GARRY. 267 pages; 22.5 × 14.5 cm. 1948. Cambridge, at the University Press; New York, The Macmillan Company. Price, \$4.00.

- Diabetic Manual for the Doctor and Patient.* 8th Ed. By ELLIOTT P. JOSLIN, M.D., Sc.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc. 260 pages; 20.5 × 14 cm. 1948. Lea & Febiger, Philadelphia. Price, \$2.50.
- Diseases of the Adrenals.* 2nd Ed. By LOUIS J. SOFFER, M.D., Associate Attending Physician, The Mount Sinai Hospital, New York City, etc. 320 pages; 24 × 15.5 cm. 1948. Lea & Febiger, Philadelphia. Price, \$6.50.
- Education for Professional Responsibility. A Report of the Proceedings of the Inter-Professions Conference on Education for Professional Responsibility held at Buck Hill Falls, Pennsylvania, April 12, 13, and 14, 1948.* 207 pages; 21.5 × 14 cm. 1948. Carnegie Press, Carnegie Institute of Technology, Pittsburgh. Price, \$3.00 (Orders should be sent to distributor, Rutgers University Press, New Brunswick, New Jersey.)
- Estudio Clínico del Enfisema Pulmonar.* By JOSE ARMANDO SCIUTO. 165 pages; 24.5 × 17 cm. (paper-bound). 1947.
- For Doctors Only.* By FRANCIS LEO GOLDEN. With a Foreword by WILLIAM E. MOUNTFORD, M.D., and illustrated by BARYE PHILLIPS. 273 pages; 21 × 14 cm. 1948. Frederick Fell, Inc., New York. Price, \$2.95.
- Hematology.* By CYRUS C. STURGIS, M.D., Professor of Internal Medicine, Chairman of the Department of Internal Medicine, University of Michigan Medical School, etc. 915 pages; 26 × 17 cm. 1948. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$12.50.
- Hope in Heart Disease: The Story of Louis Faugères Bishop, M.D.* By RUTH V. BENNETT. 307 pages; 21 × 14.5 cm. 1948. Dorrance & Company, Philadelphia. Price, \$3.00.
- An Introduction to Gastro-enterology.* 4th Ed. By WALTER C. ALVAREZ, Professor of Medicine, University of Minnesota, etc. 903 pages; 26 × 18.5 cm. 1948. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$12.50.
- List of Species Maintained in the National Collection of Type Cultures. Medical Research Council Memorandum No. 21.* 17 pages; 24.5 × 15.5 (paper-bound). 1948. His Majesty's Stationery Office, London. Price, Ninepence net.
- Mineral Nutrition of Plants and Animals.* By FRANK A. GILBERT. 131 pages; 23.5 × 16 cm. 1948. University of Oklahoma Press, Norman. Price, \$2.75.
- Pathology.* Edited by W. A. D. ANDERSON, M.A., M.D., F.A.C.P., Professor of Pathology and Bacteriology, Marquette University School of Medicine, Milwaukee. 1453 pages; 25.5 × 17.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, \$15.00.
- Physicians' Federal Income Tax Guide for the Preparation of 1948 Returns and 1949 Estimates—1948-49 Edition.* By HUGH J. CAMPBELL and JAMES B. LIBERMAN. 95 pages; 28 × 21.5 cm. (paper-bound). 1948. Doniger & Roughley, Inc., Great Neck, New York. Price, \$2.50.
- Post-mortem Appearances.* 5th Ed. By JOAN M. ROSS, M.D., B.S. (Lond.), M.R.C.S., L.R.C.P., Advisor in Pathology to the Ministry of Supply, etc. 308 pages; 17 × 11 cm. 1948. Oxford University Press, New York. Price, \$2.75.

*The Skin Diseases: A Manual for Practitioners and Students.* By JAMES MARSHALL, M.D., B.S., M.R.C.S., L.R.C.P., Consulting Dermatologist, Central Middlesex County Hospital, etc. 363 pages; 22 × 14.5 cm. 1948. Cambridge, at the University Press; New York, The Macmillan Company. Price, \$7.50.

*Tuberculosis in Childhood.* 2nd Ed. By DOROTHY STOPFORD PRICE, M.D. (Univ. Dublin), Physician, St. Ultan's Infant Hospital, Dublin, etc. With a Chapter on Tuberculous Orthopaedic Lesions and Other Contributions by HENRY F. MAC-AULEY, M.Ch., F.R.C.S.I., Orthopaedic Surgeon, Mater Misericordiae Hospital, Dublin, etc. 219 pages; 19 × 13 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$7.00.



# COLLEGE NEWS NOTES

## NOMINATIONS FOR A.C.P. ELECTIVE OFFICES, 1949-50

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1949-50, are herewith announced and published:

President-Elect ..... William S. Middleton, Madison, Wis.  
First Vice President ..... George F. Strong, Vancouver, B. C.  
Second Vice President ..... Roy R. Snowden, Pittsburgh, Pa.  
Third Vice President ..... Turner Z. Cason, Jacksonville, Fla.

Regular elections will take place at the 1949 Annual Session in New York City, March 28-April 1. The Annual Business Meeting will be held Thursday afternoon, March 31, in the Grand Ballroom of the Waldorf-Astoria Hotel.

The election of nominees shall be by the Fellows and Masters of the College. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations for members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,  
A. B. Brower, Dayton, Ohio  
Harold H. Jones, Winfield, Kans.  
Chester S. Keefer, Boston, Mass.  
T. Homer Coffen, Portland, Ore.  
Maurice C. Pincoffs, Chairman, Baltimore, Md.  
*Committee on Nominations*

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## PROPOSAL OF CANDIDATES

The By-Laws of the American College of Physicians require that candidates for election to Associateship or Fellowship shall be proposed on the official forms by Fellows from the same cities or areas as the candidates. Furthermore, these proposals must be filed at the College headquarters at least 60 days in advance of action on them by the Credentials Committee. The Committee will next meet on February 26 and 27, 1949, and will examine credentials received up to 60 days beforehand. The Committee will again meet on March 26, 1949, and November, 1949.

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## ASSOCIATES SHOULD ATTEND A.C.P. ANNUAL SESSION

Attendance at one or more Annual Sessions by Associates before proposal for advancement to Fellowship is prescribed by regulations of the Board of Regents of the American College of Physicians. This regulation was temporarily discontinued during World War II from 1942 to 1946, because it became obviously impossible for Associates in the armed services to attend and because the Annual Sessions of the College had been abandoned during part of that time. The regulation is now again in full effect. It is maintained that an Associate must display an abiding interest in the College and in internal medicine or its allied branches. There is no better way in which such an interest can be displayed than by attendance at the Annual Sessions of the College, accepted as the most important postgraduate week in the field on this Continent.

The tentative program of the 30th Annual Session, which will be held at the Waldorf-Astoria Hotel, New York, N. Y., March 28-April 1, 1949, will be published in the February issue, the Convention Number.

#### COLORADO REGIONAL MEETING ANNOUNCED

The Regional Meeting of the American College of Physicians, for its members in Colorado and their guests, will be held in Denver on March 1, 1949. Preparations for the meeting are being made by Ward Darley, M.D., F.A.C.P., Governor for Colorado, and Louis S. Faust, M.D., F.A.C.P., Chairman of Arrangements. The program will be printed and distributed to members in the State.

#### KENTUCKY REGIONAL MEETING

Members of the College, in Kentucky, and their guests enjoyed a very interesting meeting on the afternoon and evening of December 4, 1948. Held at St. Joseph's Hospital and the Phoenix Hotel in Lexington, the scientific session included speakers from a number of Kentucky cities and an address by Walter L. Palmer, M.D., F.A.C.P., Chairman of the Board of Governors of the College. Thornton Scott, M.D., F.A.C.P.; Lexington, served as Presiding Officer at the afternoon session and J. Murray Kinsman, M.D., F.A.C.P., Louisville, Governor for Kentucky, was Toastmaster at the dinner.

The scientific program was as follows:

Unusual Manifestations of Myxedema: a Case Report.

THORNTON SCOTT, M.D., F.A.C.P., Lexington.

Methods of Liver Biopsy, with Reference to a New Type of Needle.

FRANKLIN B. MOOSNICK, M.D. (Associate), Lexington.

The Addiction Liability of Keto-bemidone, a New Derivative of Demerol.

HARRIS ISBELL, M.D. (Associate), U. S. Public Health Service Hospital.  
Lexington.

Gold Therapy in Rheumatoid Arthritis.

JOSEPH T. GILBERT, JR., M.D., F.A.C.P., Bowling Green.

Unusual Instances of Hemorrhage from the Gastrointestinal Tract.

GEORGE N. BURGER, M.D., F.A.C.P., Covington.

#### EASTERN PENNSYLVANIA REGIONAL MEETING

The 11th Annual Round-up of Eastern Pennsylvanians was held in Philadelphia, December 10, 1948, under the Governorship of Edward L. Bortz, M.D., F.A.C.P., Philadelphia, who served as Presiding Officer and Toastmaster. The meeting began with a buffet luncheon at the College Headquarters and continued with a scientific program at the College of Physicians of Philadelphia, and a dinner meeting in the evening at the Warwick Hotel. The afternoon session was arranged by collaboration between Governor Bortz and Henry L. Bockus, M.D., F.A.C.P., who was currently conducting an A.C.P. postgraduate course in gastro-enterology. Approximately 400 members and their guests attended this session.

The dinner meeting was enthusiastically attended. In addition to several Governors of adjacent areas, the deans of Philadelphia medical schools were present. A.C.P. President Walter W. Palmer, and Executive Secretary E. R. Loveland addressed the gathering; and an outstanding talk on "Medicine and the National Security Resources Board" was delivered by James A. Crabtree, M.D., Director of the Medical

Service Division of the Board. For the members of Eastern Pennsylvania, Edward W. Bixby, Sr., M.D., F.A.C.P., Wilkes-Barre, presented Dr. Bortz an engraved gavel as a token of appreciation of his fine representation of the group during the past several years.

The following papers were presented during the scientific meeting:

The Prognosis in Coronary Artery Disease.

WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., Professor of Medicine,  
Woman's Medical College of Pennsylvania, Philadelphia.

Diffuse Hepatic Necrosis.

CLARK E. BROWN, M.D. (by invitation), Pathologist, Lankenau Hospital, Philadelphia.

Fat Metabolism and Vascular Degeneration.

SIDNEY WEINHOUSE, Ph.D. (by invitation), Director of Biochemical Research, Temple University Research Institute, Philadelphia.

Significant Developments in Army Medical Research.

GEORGE E. ARMSTRONG, Brigadier General (MC), USA, Deputy Surgeon General, Washington, D. C.

Differential Diagnosis of Jaundice.

HENRY J. TUMEN, M.D., F.A.C.P., Associate Professor of Gastroenterology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

The So-called Post-Cholecystectomy Syndrome.

HENRY L. BOCKUS, M.D., F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

The Physiologist's Concept of Biliary Dyssynergia.

S. S. KETY, M.D. (by invitation), Professor of Clinical Physiology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

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The 77th Annual Meeting of the American Public Health Association will be held in New York City the week of October 23, 1949.

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THE AMERICAN BOARD OF PEDIATRICS, INC.; John McK. Mitchell, M.D., Executive Secretary; 6 Cushman Road, Rosemont, Pa. Oral examinations will be held at St. Louis, Mo., on February 17, 18 and 19, 1949, and at Baltimore, Md., on May 7, 8 and 9, 1949.

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#### HOTEL ACCOMMODATIONS, 30TH ANNUAL SESSION

Directions and forms for making hotel reservations during the 30th Annual Session, New York City, March 28-April 1, 1949, were mailed to all members of the College during December. It is hoped that the members will follow these directions and will enter their reservations at the earliest possible moment so as to assure themselves of the type of accommodation desired. An adequate number of rooms has been provided; however, the hotels will appreciate it if arrangements are made, whenever possible, for occupancy of rooms accommodating two persons.

Reservations will be acknowledged by direct confirmation from the hotels. If an applicant subsequently finds it impossible to attend the session, he is requested to

send notification promptly to the Housing Bureau, The American College of Physicians, c/o New York Convention Bureau, 500 Park Avenue, New York 22, N. Y.

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The American College of Physicians makes grateful acknowledgment of the contribution by Cyrus C. Sturgis, M.D., F.A.C.P., to the College Library of Publications by Members, of a copy of his book, "Hematology," published by Charles C. Thomas, Springfield, Ill., 1948.

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#### MISSISSIPPI VALLEY MEDICAL SOCIETY 1949 ESSAY CONTEST

The Ninth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1949. The Society will offer a cash prize of \$100.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents and citizens of the United States. The winner will be invited to present his contribution before the Fourteenth Annual Meeting of the Mississippi Valley Medical Society to be held in St. Louis, Mo., Sept. 28, 29, 30, 1949, the Society reserving the exclusive right to first publish the essay in its official publication—the *Mississippi Valley Medical Journal* (incorporating the *Radiologic Review*). All contributions shall be typewritten in English in manuscript form, submitted in five copies, not to exceed 5000 words, and must be received not later than May 1, 1949. The winning essays in the 1948 contest appear in the January 1949 issue of the *Mississippi Valley Medical Journal* (Quincy, Illinois).

Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

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#### ADDITIONAL LIFE MEMBERS

The American College of Physicians takes pleasure in announcing that the following Fellows have become Life Members of the College by their recent subscriptions:

Joseph Hughes, M.D., Philadelphia, Pa.  
George B. Dorff, M.D., Brooklyn, N. Y.  
G. A. Westfall, M.D., Halstead, Kans.  
Milford O. Rouse, Dallas, Tex.

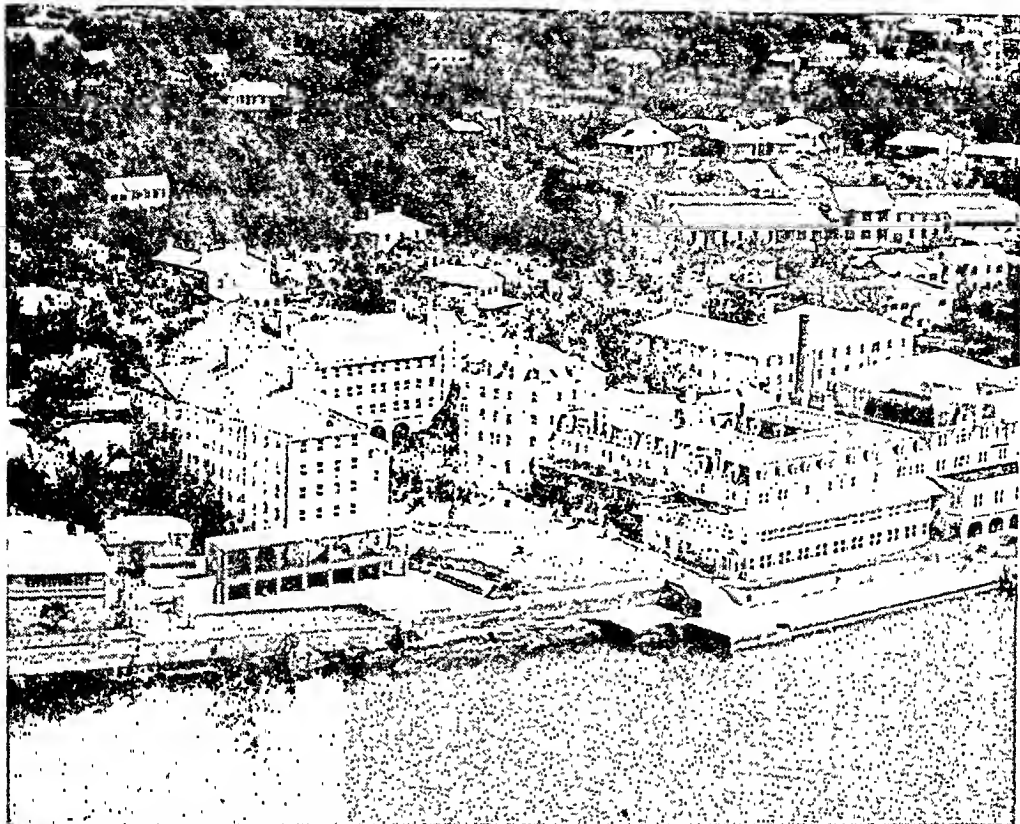
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#### POST-CONVENTION CRUISE TO BERMUDA

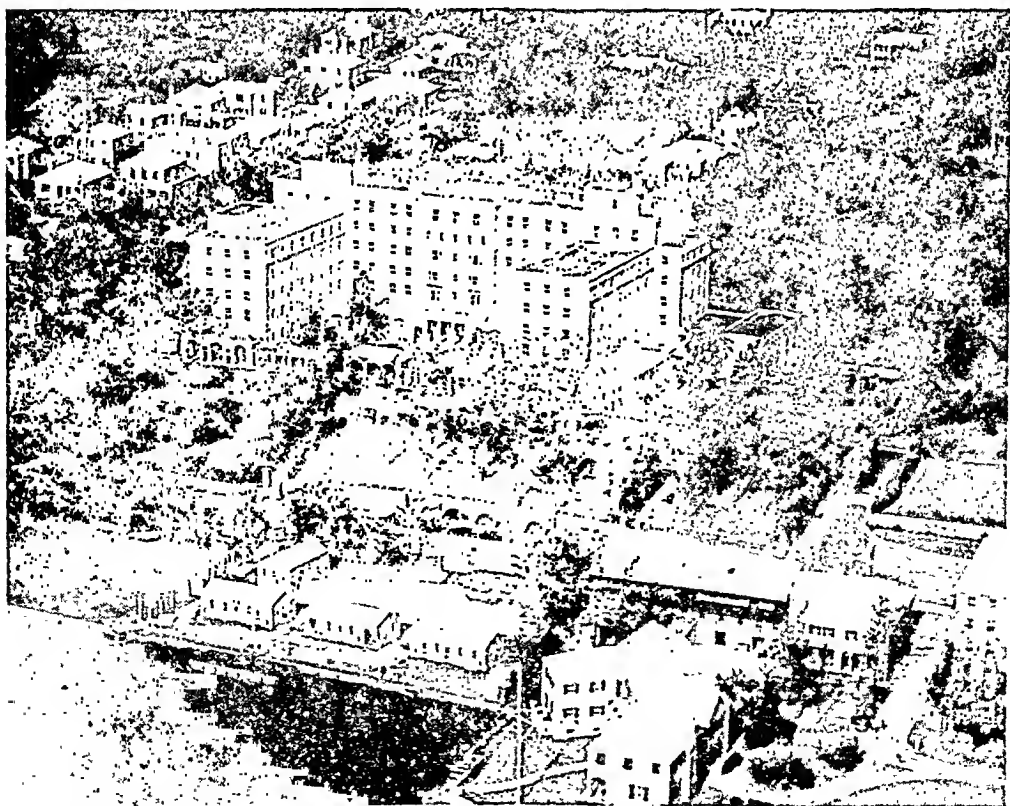
You are in "Merrie England" as soon as you leave the Pier in New York and you will be under the flag of Great Britain until your return.

You will enjoy the new *Queen of Bermuda*, the spacious lounges, the cozy settings for chats, quiet reading, or spicy cocktails. The stewards take pride in carrying out the tradition of courtly service. The food is international, prepared by chefs trained in the best restaurants of Europe. Whether you order veal and ham pie, a Yorkshire pudding, chicken Maryland, or other traditional dish, you will enjoy it.

We shall use two hotels in Bermuda. The Princess stands at the water's edge. The Bermudiana stands on a small bluff directly above the blue waters. These hotels are the best in the islands. Both have magnificent views overlooking the lovely harbor and hills beyond and are only five to ten minutes by pleasant walks from the fascinating shops.



The Princess Hotel and guest cottages, overlooking the blue waters of Hamilton Harbor, just west of the city.



The newly-opened Bermudiana Hotel, well known to Bermuda's visitors. In lower right-hand corner, the Royal Bermuda Yacht Club.

Bermuda is intriguing, beautiful, picturesque, irresistible. It is a land of cedars and blossoms; sloping green hillsides; charming bays and beaches; of white and pastel coral cottages; and a tempo that makes you forget time and care. The Easter lilies, the bougainvillae, the hibiscus and the Bermuda morning glory will greet you.

The cruise itinerary gives you two and a half days in Bermuda. You may extend your stay if you so desire. While there, you will want to visit the Sea Gardens where coral polyp still shapes its strange life under the water in fans, rods and many fantastic shapes. You will also want to visit the spectacular caves, Leamington and Crystal. The latter is viewed for the most part from pontoon bridges. The water giving back the overhead reflections makes it a place of bewildering beauty.

Decide now and go. You will benefit by a decision *now*. The accommodation at all rates is limited and the demand for Bermuda space in the Spring is always very heavy. If you see any possibility of going, make your reservation; cancel later if you must. Yes, your money back, of course!

For answers to your questions, plan of ship, Bermuda booklet, etc., write AT ONCE to Leon V. Arnold, 36 Washington Square West, New York 11, N. Y. Mr. Arnold was our cruise director in 1938 and will accompany the party this year.

## OBITUARIES

## DR. EDWARD RHODES STITT

Edward Rhodes Stitt, Rear Admiral, Medical Corps, United States Navy, Retired, a Fellow of the American College of Physicians since 1923 and member of the Board of Regents from 1923 to 1926, died in the U. S. Naval Hospital, Bethesda, Md., on November 13, 1948, in his 81st year.

Dr. Stitt acquired his early education in a private school, and later entered the University of South Carolina where he gained his A.B. degree in 1885. He then transferred to the University of Pennsylvania and studied under Sir William Osler, graduating with the degree of Doctor of Medicine in 1889. He was accepted in the Medical Corps of the Navy upon graduation and commissioned Assistant Surgeon in March, 1889, his first commission being signed by President Benjamin Harrison. His first few years in the Navy were spent in assignments ashore and afloat, including duty in the *U.S.S. Baltimore*, one of the vessels of the famous "White Squadron," when that crack cruiser sailed for Valparaiso during the Balmacedist uprising in Chile.

In August, 1896, he was on duty in the Bureau of Medicine and Surgery where he served during the Spanish American War. In 1902 he was selected as instructor of tropical medicine and bacteriology at the newly established Navy Medical School in Washington, D. C. In 1905 he was ordered to London where he studied under Sir Patrick Manson at the famous London School of Tropical Medicine, graduating with distinction from that school. After completing the course, he went to Manila, Canacao, and Olongapo, Philippine Islands, and to Guam, Yokohama and Honolulu, in connection with the study of tropical diseases.

He was promoted to the rank of Rear Admiral in 1917. In 1920 he was selected by President Wilson to be Surgeon General of the Navy, and was reappointed in 1924 by President Coolidge. He was Inspector of Medical Department Activities of the West Coast during his last three years of active duty, retiring from active duty in 1931, after 42 years service. During his administration as Surgeon General he devoted much attention to hospital administration, and aviation medicine was established as an official specialty.

As a teacher of tropical medicine at the newly established Navy Medical School, he did much to make this the principal center for the study of tropical diseases in the United States, and the leading school of postgraduate instruction for medical officers in this specialty. Concurrently with his duties at the Medical School, he was professor of tropical medicine at both George Washington and Georgetown Universities, and also delivered frequent lectures on tropical medicine at the Jefferson Medical College of Philadelphia.

Admiral Stitt was the author of "Diagnostics and Treatment of Tropical Diseases," and of "Practical Bacteriology, Hematology and Parasitology," the latter now in its 10th edition, both published by The Blakiston Company; and he made many contributions to medical literature.

He was associate professor of medical zoölogy in the University of the Philippines; and, from 1941, he held appointment as consultant in tropical medicine to the Secretary of War. A former president of the National Board of Medical Examiners, he was a member of the Federal Board of Hospitalization and of executive and central committees of the American Red Cross.

The many honors and awards received by Admiral Stitt included the Navy Cross, "for exceptionally meritorious service in the duty of great responsibility in connection with the U. S. Navy Medical School, and in connection with the general sanitation and military work at the school and throughout the service"; he held honorary degrees of LL.D., University of South Carolina, 1917, and University of Michigan in 1921;

Sc.D., Jefferson Medical College of Philadelphia, 1920, and University of Pennsylvania, 1924; Ph.M., Philadelphia College of Pharmacy and Science, 1921. In 1942 he received the Gorgas medal from the Association of Military Surgeons. The citation accompanying the presentation read in part, "To a distinguished scholar and authority of international fame in tropical medicine." He was also a recipient of the Theobald Smith and Richard Pearson Strong medals.

Admiral Stitt was a past president of the Association of Military Surgeons of the United States and American Society of Tropical Medicine; a member of American Association of Immunologists, Association of American Physicians, American Public Health Association, Royal Society of Medicine, and Southern Medical Association; a fellow of the American Medical Association.

The Navy Medical Corps' premier physician, officer and gentleman, scientist, author and scholar, the personification of the thought embodied in the verse entitled "The Things That Are Most Excellent":

"The grace of friendship—mind and heart  
Linked with their fellow heart and mind;  
The gains of science, gifts of art;  
The sense of oneness with our kind;  
The thirst to know and understand,  
A large and liberal discontent;  
These are the goods in life's right hand,  
The things that are more excellent."

PAUL F. DICKENS (MC), USN, Retired, F.A.C.P.

#### DR. JOSEPH FRANCIS BREDECK

Dr. Joseph Bredeck exercised a highly important influence in the field of public health in St. Louis from 1920 to 1925, when he was Controllor of Tuberculosis, and later as Health Commissioner, from 1933 to the time of his death, October 4, 1948.

In this latter position he was widely recognized for his persistent efforts in the direction of improving the public laws pertaining to health. His name is honored chiefly for two important contributions: first, the establishment of a model milk ordinance, which, while it resulted in much controversy on the part of producers and dairies, was nevertheless in the public interest; second, for his clean restaurant law which had an immediate and drastic effect of converting the previously filthy places into clean agencies for the dispensing of food.

Dr. Bredeck was 58 years old at the time of his death. He received his A.B. at Christian Brothers College in 1910, and his M.D. from Washington University in 1914. He received the degree of D.P.H. from the University of Pennsylvania in 1917. He spent a year in the Henry Phipps Institute in Philadelphia, and later in Germany.

He saw service in World War I from 1917 to 1919. Formerly an Instructor in Washington University School of Medicine, he later became Director of the Department of Public Health of St. Louis University. He was a member of the St. Louis and Missouri Medical Societies, and the American Medical Association, National Tuberculosis Association, and was elected a Fellow of the American College of Physicians in 1929.

His departure from the scene at a relatively early age emphasized the loss which the community of St. Louis suffered. The American College of Physicians deeply regrets the loss of such an outstanding member.

RALPH KINSELLA, M.D., F.A.C.P.,  
Governor for Missouri



## DR. ROSS McCLURE CHAPMAN

On September 24, 1948, Baltimore and the State of Maryland suffered a great loss in the death of Dr. Ross McClure Chapman, of Towson, Md.

Dr. Chapman was born in Belleville, N. Y., on July 13, 1881. He attended Union Academy and Syracuse University, and took his medical degree in 1905 at the University of Michigan. Following his internship in the Utica, N. Y., State Hospital, he became Junior Physician in the Binghamton State Hospital (1908-16) and then went to St. Elizabeths Hospital, Washington, D. C., where, from 1916 to 1919 he progressed from Assistant Physician to Clinical Director. From 1920 on he served as Medical Superintendent of the Sheppard and Enoch Pratt Hospital, in Towson. It must be mentioned here that, under his supervision, the work at the Sheppard and Enoch Pratt Hospital grew in scope and value to the community. Along with this, Dr. Chapman was Professor of Psychiatry in the University of Maryland School of Medicine, and many fine students have followed in his footsteps from his teachings.

Dr. Chapman was a diplomate of the American Board of Psychiatry and Neurology, a past president of the Washington Psychoanalytic Society, the American Psychopathological Association, and the American Psychiatric Association. He was also a member of the Washington Society of Mental and Nervous Diseases, the American Psychoanalytic Association and the American Medical Association. He was a consultant in psychiatry to the U. S. Public Health Service from 1940 on. Dr. Chapman was elected to Fellowship in the American College of Physicians in 1931.

The last two years of his life were kept up to the best of his ability under the great handicap of a cardiovascular situation. His loss to our community will be hard to replace.

WETHERBEE FORT, M.D., F.A.C.P.,  
Governor for Maryland

## DR. RALPH BERNSTEIN

The death of Dr. Ralph Bernstein in Philadelphia, on November 19, 1948, brought a great sense of loss to his many friends and patients, but especially to his colleagues at the Hahnemann Medical College where he had been Professor of Dermatology since 1915.

Dr. Bernstein was born in Columbia, Pa., on April 12, 1877. He received his M.D. degree from the University of Pennsylvania School of Medicine in 1903, and also from Hahnemann Medical College and Hospital of Philadelphia in 1904, the staff of which institution he joined the same year.

Dr. Bernstein has been Consulting Dermatologist to the Shriners' Hospital for Crippled Children and Women's Homeopathic Hospital, in Philadelphia; Allentown State Hospital; J. Lewis Crozer Home for Incurables and Homeopathic Hospital, in Chester; Homeopathic Hospital, Pottstown; Homeopathic Hospital of Chester County, West Chester; West Jersey Homeopathic Hospital, in Camden. A Fellow of the American College of Physicians since 1920, Dr. Bernstein was a member of the American Academy of Dermatology and Syphilology, Society for Investigative Dermatology, American Association for the Advancement of Science, American Editors and Authors Association, American Academy of Political Science, and various state and local homeopathic societies. He was the author of four textbooks on skin diseases, and had contributed more than one hundred articles to medical journals.

Dr. Bernstein's memory will be cherished by many people, and his influence will long be felt by the physicians who trained under him.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

## DR. GEORGE WILLIAM ROSS

Dr. Ross, who became a Fellow of the American College of Physicians in 1927, died on June 13, 1948, after a lengthy illness which compelled his retirement from active practice in 1933.

Born in Strathroy, Ont., in 1877, the youngest son of Hon. Sir George and Lady Catherine Ross, he was educated in Upper Canada College and the University of Toronto, graduating in Medicine in 1902. He pursued postgraduate studies in England, notably under Sir James MacKenzie in cardiology and Sir Almroth Wright in immunology. On returning to Toronto, he joined the staff in therapeutics, and carried on private practice until ill health compelled his retirement.

Dr. Ross was a member of the Royal College of Physicians of London, and the Canadian, Ontario and British Medical Associations. He was a former vice-president of the American Immunological Association. His wife predeceased him some years ago and his two sons lost their lives in World War II.

Possessed of a keen, inquisitive mind, and a genial disposition, Dr. Ross will be greatly missed by his colleagues and friends, and his death is a distinct loss to the medical profession.

H. K. DETWEILER, M.D., F.A.C.P.,  
Governor for Ontario

## DR. W. GRADY MITCHELL

Dr. W. Grady Mitchell of San Angelo, Tex., died in Seattle, Wash., on October 8, 1948. He had had one or two myocardial infarcts earlier in the year.

Dr. Mitchell was born in Franklin County, Va., July 17, 1896. He graduated from the University of Tennessee College of Medicine in 1921, and served his internship at the Philadelphia General Hospital, 1921-24. Following this, Dr. Mitchell pursued postgraduate studies at the University of Pennsylvania and in England, Germany and Austria. He then became physician to the Pennsylvania Hospital, which position he occupied from 1930 to 1935. He was an instructor in medicine in the University of Pennsylvania School of Medicine during this time. In the latter year, he removed to San Angelo and became cardiologist and director of clinical laboratories of St. John's Hospital. He was, also, a member of the staff of the Shannon West Texas Memorial Hospital of that city. He served as a Lieutenant Commander, United States Naval Reserve, 1940-44. Dr. Mitchell served as president and secretary of Tom Green Eight Counties Medical Society; he was a member of the Texas Heart and Southern Medical Associations, and a fellow of the American Medical Association. Since 1939 he had been a Fellow of the American College of Physicians.

Dr. Mitchell was highly esteemed and enjoyed a large consultation practice in cardiology. He is mourned by a host of friends, professional and lay, who miss his genial personality and individualism for which he will be long remembered.

DAVID W. CARTER, JR., M.D., F.A.C.P.,  
Governor for Texas

## DR. MANFRED KRAEMER

Manfred Kraemer, M.D., a Fellow of the American College of Physicians since 1935, died in Newark, N. J., on Friday, November 12, 1948, in his forty-fourth year. His death was due to coronary occlusion.

He was a native of New Jersey and received his college and medical degrees from the University of Pennsylvania. He interned at the Newark City Hospital, following which he entered the practice of internal medicine and gastro-enterology in Newark.

He did extensive postgraduate work at the University of Vienna and the London School of Tropical Medicine. He was certified by the American Board of Internal Medicine in internal medicine and gastro-enterology. He rose in prominence quickly and was recognized as one of the outstanding gastro-enterologists in the State.

Dr. Kraemer was visiting physician and chief of the Gastrointestinal Department of the Newark Presbyterian Hospital, gastroenterologist to St. James Hospital, and associate visiting physician, Newark City Hospital. He was a consultant at the Irvington General Hospital. He was formerly an instructor in the New York Medical College and a postgraduate lecturer at New York University.

He was a member of many societies including the Academy of Medicine of Northern New Jersey; Royal Society of Tropical Medicine and Hygiene (England); International Gastro-Enterological Society; American Gastro-Enterological Association; American Society of Tropical Medicine; Association of Military Surgeons; and the American Gastroscopic Club.

Early in World War II, Dr. Kraemer enlisted and served as a Lieutenant Colonel in the Medical Corps, A.U.S. He was chief of the gastro-intestinal service, 188th General Hospital, and chief of medical service, 121st and 242nd General Hospitals.

He wrote numerous articles on gastro-enterology which appeared in various medical journals. He was very active in many of the organizations with which he was connected and appeared frequently on the programs as a speaker.

Dr. Kraemer was an earnest and conscientious worker in internal medicine; his chief interest, however, lay in diseases of the gastrointestinal tract. He was a skilled physician, highly regarded in his community. His high standards in life and in the practice of medicine deepen the loss of his passing to his family and the community.

JEROME G. KAUFMAN, M.D., F.A.C.P.

#### DR. ALVA BROWN CRADDOCK

Alva Brown Craddock, M.D., F.A.C.P., died July 29, 1948, after an illness of eight months.

Dr. Craddock was born in Jackson's Gap, Ala., January 26, 1889. He attended Howard College in Birmingham where he obtained the degrees of B.S., 1908, and M.S., 1909. In 1911 he entered Johns Hopkins University and, after three years of study, was forced to leave because of illness. He returned to Johns Hopkins and received his M.D. degree in June, 1918. Following graduation he was given a scholarship in the Trudeau School of Tuberculosis and later joined the staff of the Metropolitan Life Insurance Company's Hospital at Mount McGregor, N. Y., where he remained four years as pathologist. The following year he was pathologist at New York State Hospital, Ray Brook, and then became associate resident in medicine at the Albany City Hospital, Albany, N. Y. He moved to Asheville, N. C., and began the private practice of medicine in 1924. He served on the staffs of Asheville Memorial Hospital and Biltmore Hospital.

Dr. Craddock was a member of the Buncombe County Medical Society, Medical Society of the State of North Carolina, Southern and American Medical Associations. He had been a Fellow of the American College of Physicians since 1930.

Dr. Craddock was naturally modest and retiring, but his absolute sincerity and honesty won for him the respect and affection of those who knew him. Because of his professional acumen, keen insight and common-sense application of his knowledge, he was recognized as an outstanding physician and diagnostician of western North Carolina. He will be sorely missed by his colleagues and patients.

WALTER R. JOHNSON, M.D., F.A.C.P.



A historic view of the southern tip of Manhattan Island from the East River.

## NEW YORK AS A MEDICAL CENTER \*

To the average non-New-Yorker, America's largest city is a city of machines, of crowds and indifference. He is appalled by the contrast with his own community, in that here each person apparently goes his own way with little regard for the needs, wants and welfare of others. The friendliness and warmth of his own home town is lacking. But that is the New York which one gets to know only from short and casual observation.

The warmth, spirit and heart of the Big City of O. Henry, Mark Hellinger and Damon Runyon can be fully understood only by those who know New York intimately. There is no better objective evidence of our high regard for human life and welfare than in our medical services. Exclusive of federal and state hospitals, there are at present within the boundaries of New York City proper 145 hospitals. Of these, 85 are under voluntary auspices, 14 are maintained by the city, and 46 are proprietary. They have a combined total of 32,071 beds, of which 9,232 are in municipal hospitals, 19,441 in voluntary hospitals, and 3,398 in proprietary institutions.

In THE MASTER PLAN FOR HOSPITALS AND RELATED FACILITIES issued by the Hospital Council of Greater New York, it was reported that in 1946 there were four hospitals with 882 beds for communicable diseases, all under municipal auspices. An additional 76 beds were available as an assigned service of a general hospital, and 35 general hospitals had 105 beds classified as isolation facilities. The number of days of hospital care for communicable diseases has dropped from 244,686 in 1940 to 116,856 in 1945.

In 1946, there was a total of 20 hospitals providing services for the care of patients with tuberculosis, with 16 of the hospitals with 4,495 beds within New York City. The number of new cases of tuberculosis in New York City dropped from 9,466, or a rate of 129.8, in 1935, to 7,062, or a rate of 91.4, in 1945. Deaths from tuberculosis dropped from 4,371, or a rate of 59.9, to 2,513, or a rate of 45.4, during the period, and total patient-days for care of the disease dropped from 1,972,698 to 1,803,549.

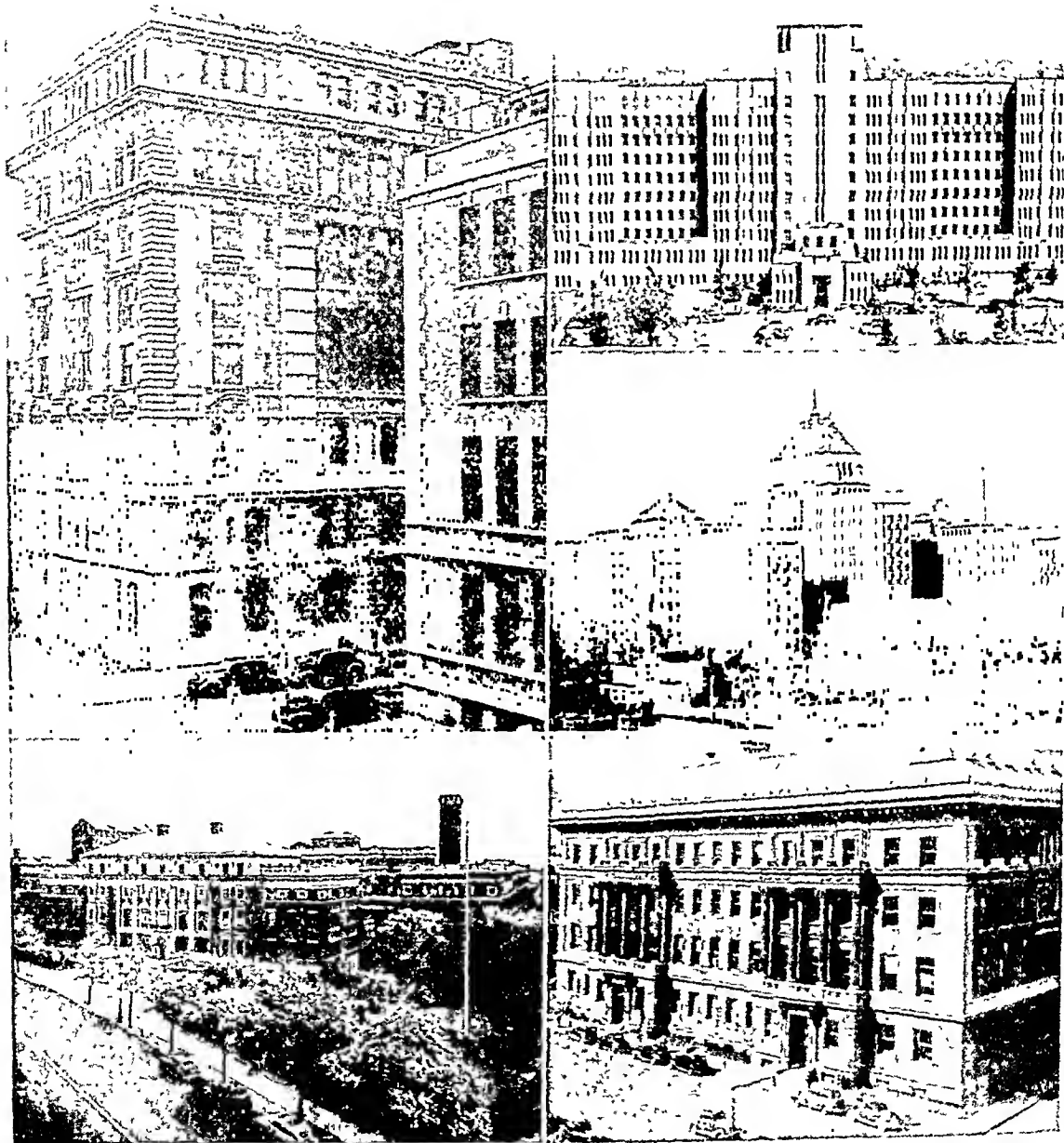


Waldorf-Astoria Hotel  
General Headquarters.

\* This article was contributed by the Committee on Publicity, 30th Annual Session.

Illustrations for this article were generously provided by the New York Convention and Visitors' Bureau.

Most of the beds for the care of patients with mental disease are provided by the State. Eleven hospitals, with a bed capacity of 11,895 beds, are located within New York City. One of these, with 89 beds, is part of a voluntary hospital, and two municipal hospitals, with 705 beds, are operated in connection with general hospitals. A total of 42 hospitals, with 39,819 beds, are available to residents of New York City.



Top Left: Polhemus Memorial Clinic of Long Island College of Medicine, Brooklyn.  
 Top Right: Queens General Hospital, Jamaica—a newer city hospital.  
 Center Right: Kings County Hospital, Brooklyn—one of New York's largest.  
 Bottom Left: Montefiore Hospital.  
 Bottom Right: New York University College of Medicine.

The first city in America to establish a convalescent home, New York has 37 such homes or institutions, with 2,379 beds, all under voluntary auspices, which provide facilities for the care of convalescent patients. Only 10 of the homes, with 502 beds, are in New York City, and only one, with 60 beds, is a branch of a general hospital.

New York was also the first city to have a specialized hospital for chronic disease. Established in 1884 as a tribute to the 100th birthday of Sir Moses Montefiore, the revered British philanthropist, the original Montefiore Home provided 26 beds for the care of chronic invalids. The Goldwater Memorial Hospital for Chronic Disease, a 1500 bed institution erected on Welfare Island in 1939, is the first municipal hospital of its type. New York has 13 institutions, with 4,701 beds, which are devoted to patients with long-term illnesses. Twelve of the institutions, with 3,201 beds, are under voluntary auspices; the other is Goldwater. In addition, about half of the facilities provided in homes for the aged and in City Home and Farm Colony, and 1,770 beds in private nursing homes are used for this type of care. However, a large percentage of the beds in general hospitals are now occupied by patients who would use facilities for the care of long-term illnesses if they were available. Some 22.5 per cent of the general-care beds in municipal hospitals are occupied by such patients. The New York City Department of Hospitals, however, has recently started a home-care program patterned after the successful demonstration of Montefiore Hospital, which, it is hoped, will reduce the number of such patients now occupying general-care beds.

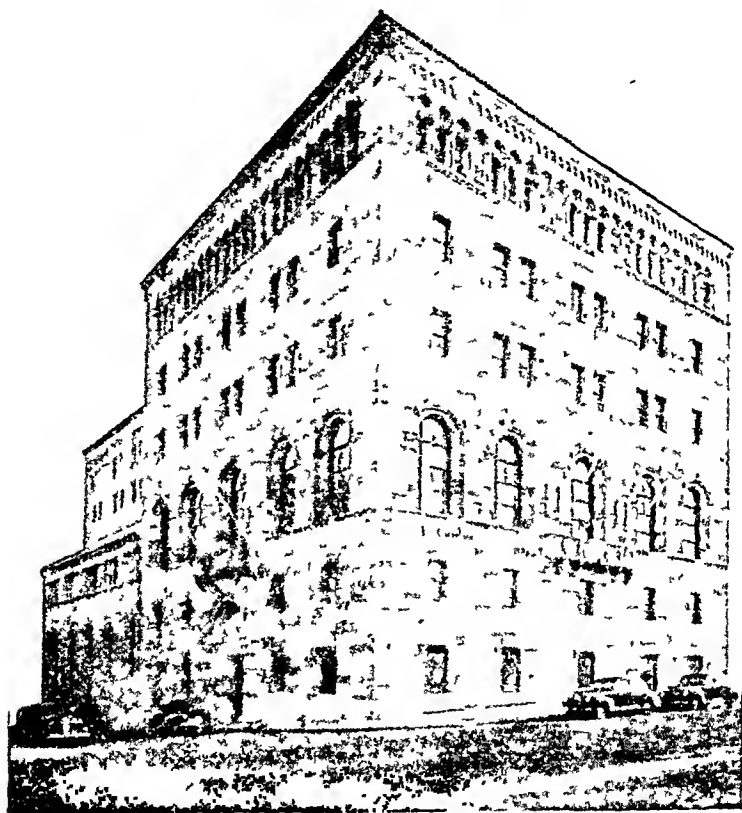
In 1947, 914,928 patients were treated in New York City hospitals, 518,116 in voluntary hospitals, 266,994 in municipal hospitals and 129,818 in proprietary hospitals. They spent a total of 12,441,036 patient days, 6,034,266 of which were in voluntary hospitals, 5,531,232 of which were in municipal hospitals, and 875,538 of which were in proprietary hospitals. The average length of stay of general medical-care patients was 12.4 days. Patients in voluntary hospitals averaged 10.7 days as compared with 15.6 days in municipal hospitals. In addition, 6,151,180 visits were made to out-patient services, 3,428,157 of which were to the out-patient departments of voluntary hospitals. Our ambulances made over 300,000 calls last year. During the war period, ambulance attendants were used in the ambulance service rather than physicians, but within the last three months internes have started to ride the ambulances again.

Of the 28,584 beds in 113 general-care hospitals in 1946, 4,364, or 15.3 per cent, were one-person rooms; 3,586, or 12.6 per cent, were in two-bed rooms; 1,497, or 5.2 per cent, were in three-bed rooms; 2,612, or 9.1 per cent, were in four-bed rooms; and 16,525, or 57.8 per cent, were in rooms with more than four beds. Of the 18,761 beds in voluntary hospitals, 20 per cent were one-bed rooms and 47.1 per cent were in rooms with more than 4 beds. Only 3.4 per cent of 8,096 beds in municipal hospitals were in one-person rooms as compared with 88.6 per cent in rooms with more than four



beds. In the proprietary hospitals, 18.9 per cent of the beds were in one-person rooms, and 29.8 per cent in wards of more than four beds.

There is a marked similarity between the voluntary and proprietary hospitals in the percentages of their respective bed complements allocated to general medicine and surgery, and those unassigned. A relatively small proportion of the total complement of beds is assigned to the medical and surgical specialties. In 1946, sixteen general hospitals reported a total of 720 beds allocated to orthopedic patients. Of the 1,432 beds assigned to eye, ear, nose and throat patients, 640 were in six hospitals devoted solely to these specialties.



New York Academy of Medicine.

New York has approximately 18,000 registered physicians, more than the States of Alabama, Arizona, Arkansas, Colorado, Delaware, Idaho, Maine, Montana, Nevada, New Hampshire, New Mexico, North Dakota, Rhode Island, South Dakota, Utah, Vermont, Wyoming, Mississippi, Nebraska, Oregon and South Carolina, combined. Many of these physicians are graduates of our five medical schools: The Columbia University College of Physicians and Surgeons, 622 West 168th Street; Cornell University Medical College, York Avenue at 69th; New York University College of Medicine, 477 First Avenue; Long Island College of Medicine, 350 Henry Street,





Top Left: Hospital of the New York Medical College Flower and Fifth Avenue Hospitals.

Top Right: Lenox Hill Hospital.

Bottom Left: College buildings of the New York Medical College Flower and Fifth Avenue Hospitals.

Bottom Right: Child in Cerebral Palsy Clinic, Lenox Hill Hospital.

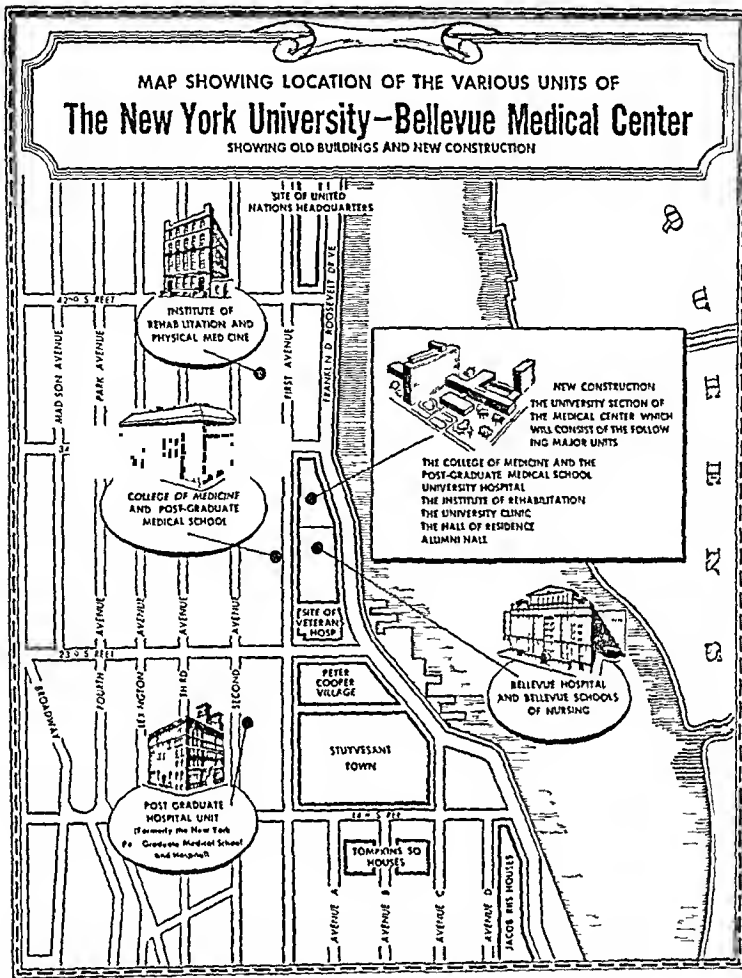
Brooklyn; and the New York Medical College, 105th Street and Fifth Avenue. The oldest of the schools is Columbia University College of Physicians and Surgeons, which had its origin in a school of medicine established in 1767 in connection with King's College. We have two great medical centers in the Columbia-Presbyterian Medical Center and the Cornell Medical Center, and are now witnessing the development of a third, The New York University-Bellevue Medical Center. Announcement has recently been made of the merger of New York Post-Graduate Medical School with New York University.

Center of professional medical activities in New York is the New York Academy of Medicine, which observed its centennial last year. Located at 2 East 103rd Street, the Academy of Medicine is headquarters for many local and national medical organizations. Its medical library, the second largest collection of medical literature in the United States, was recently presented with what has been termed by authorities "the world's first scientific document." It is the Edwin Smith Papyrus, a treatise written by an Egyptian physician 4,600 years ago, in which he deals with clinical observation, diagnosis, prognosis and treatment.

New York's interest and leadership in providing medical services dates back to the time when it, too, was a small village. In 1714, when New York was a city of but 8,000 persons, six members of the Common Council met to consider the establishment of a city institution. The institution, which was known as The Publick Workhouse and House of Correction, was built in 1736 on the site of the present City Hall, and was one room measuring 23 by 25 feet, with six beds. To accommodate the ever-increasing numbers of the needy, new buildings were erected, and as the hospital section of the workhouse had become its largest department, it was incorporated as Bellevue Hospital in 1811. By 1848, Bellevue Hospital had become an important teaching institution, and in 1861 a medical school was opened in conjunction with the hospital. This school was combined in 1898 with the New York University College of Medicine which had been started in 1841.

The second oldest general hospital in the nation (the Pennsylvania Hospital was established in Philadelphia in 1751) is New York Hospital, now a part of the Cornell Medical Center. Incorporated in 1771 by the Society of the Hospital of the City of New York, New York Hospital was built in 1775. According to E. H. L. Corwin in his "The American Hospital," "Its inception was due to the efforts of Drs. Samuel Bard and John Jones who thought hospitals afforded the best and only means of properly instructing pupils in the practice of medicine."

That Dr. Bard's concept is widely followed today is shown by the fact that more than 10 per cent of all the internes in this country are receiving training in New York City hospitals. In 1946, New York City had 145 general-care hospitals, with 32,071 beds. Not including Memorial Hospital, which is considered a specialized cancer hospital, 37 of these hospitals,

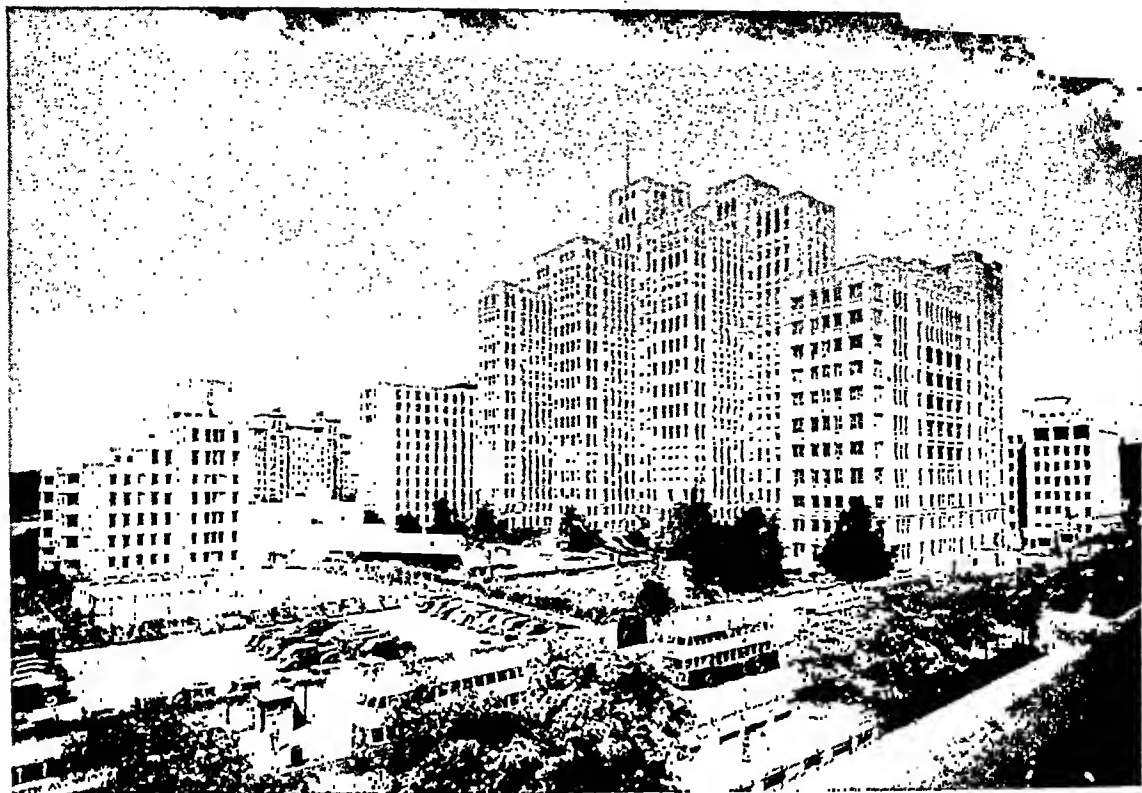


with a total of 24,040 beds, are approved for residency training, and 34.5 per cent of our hospitals are approved for residency training in both medicine and surgery.

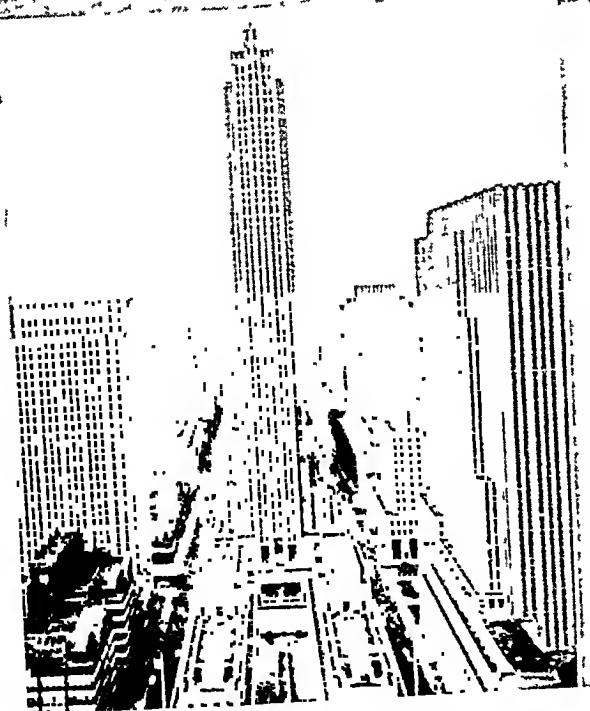
Although many hospitals were built before 1860, the greatest growth was following the Civil War. During this period, there was a decided change in public attitude toward hospitals, and they were no longer regarded as institutions for the poor, but were patronized by patients who were able to pay for services. Organized under the auspices of Archbishop Hughes in 1849 by The Sisters of Charity of St. Vincent, St. Vincent's Hospital, the first denominational hospital in the city, was also the first to provide private rooms for private patients.

These are but a few of our many old and new medical institutions and services.

Since the American College of Physicians last met here ten years ago, there have been many changes in our city. New and great medical services and institutions, such as The Public Health Research Institute of the City of New York, Inc., the Sloan-Kettering Institute of Cancer Research, the Montefiore and Department of Hospitals home-care programs, the United



Top: The Columbia-Presbyterian Medical Center.  
Bottom: The New York Hospital-Cornell Medical Center.



Top: Situated in the heart of the city and surrounded by skyscrapers is beautiful Central Park.  
Bottom Left: Towering Rockefeller Center.  
Bottom Right: Statue of Liberty.

Medical Service and Health Insurance Plan of New York, and the Hospital Council of Greater New York, have been started. We stand on our record of medical services to prove that we are not a cold, cynical metropolis, but a community which, despite its size and complexity, places the highest possible premium on the health and welfare of its citizens.

That warmth and understanding is shown not only in our medical services, but also in our many other activities which are of particular interest to our visitors. The general headquarters of the 30th Annual Session, the Waldorf-Astoria, is the center of many activities. Stretching from the towering Empire State Building at 34th Street up to Central Park at 59th Street, is famous Fifth Avenue, style and shopping center of the nation. On up Fifth Avenue, at the corner of 82nd Street, is the Metropolitan Museum of Art, and a few blocks beyond, at the corner of 104th Street, just past the Academy of Medicine, is the Museum of the City of New York. Across the park, on Central Park West and 79th Street, is the American Museum of Natural History and Hayden Planetarium. The especially fascinating Museum of Modern Art, at 11 West 53rd Street, is just a few blocks from the headquarters.

At 50th Street on the Avenue of the America's, which New Yorkers still call Sixth Avenue, is Rockefeller Center and Radio City, home of many of the nation's radio and television broadcasts. Visitors may also be interested in the Museum of Science and Industry, which is located here. Moving on westward is the most famous of all New York sights—Broadway and the heart of the theatre district.

To list all of New York's fabulous attractions is impossible. Information on them will be available at the headquarters; or you can just ask any New Yorker. The chances are that you will find he, too, came originally from Kansas, Iowa, Alabama or Texas.

# ANNALS OF INTERNAL MEDICINE

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## DIAGNOSTIC SIGNIFICANCE OF URINARY HORMONAL ASSAYS: REPORT OF EXPERIENCE WITH MEASUREMENTS OF 17-KETO-STERIODS AND FOLLICLE STIMULATING HORMONE IN THE URINE \*

By ROBERTO F. ESCAMILLA, M.D., F.A.C.P., *San Francisco, California*

### HISTORY

THE discovery that extracts of human urine have measurable androgenic and estrogenic effects has stimulated many investigators. Concepts worked out by years of clinical observations seemed possible of more definite proof or disproof. Estimating the values of excretion products of endocrine function in the urine promised a way to study further these established clinical syndromes in the human patient rather than in the experimental animal.

However, bioassay is necessary in many of the determinations. This usually means maintaining animal colonies with all the attendant complications, and the necessity for specially trained personnel. Also various animal species do not react alike to similar stimuli and of course results are not always transferable to humans. All of these factors have limited the widespread acceptance and availability of many of the tests for clinical use—with the obvious exception of the pregnancy tests.

However, with the introduction of a chemical test in which animals were not necessary and in which a color reaction gave a sensitive end-point, there was renewed and more general interest in measuring urine hormone excretion. The test alluded to is that for steroids, introduced by Zimmermann in 1935<sup>1</sup> as a test for "androgens." He showed that substances with an active methylene group ( $\text{CH}_2\text{CO}$ ) produced a red color with meta-dinitrobenzene and KOH which may be measured quantitatively. 17-Ketosteroids, that is,

\* Presented before the Twenty-ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948.

From the Division of Medicine, University of California Medical School, San Francisco, California.

steroids with a ketone group at the 17th carbon atom, produce this color reaction. Estrone is a 17-ketosteroid but can be excluded from the test by washing out the acid phenolic fraction with alkali. The neutral 17-ketosteroids which remain, and which are measured, are primarily the excretion products of testosterone and certain adrenal steroids. Further subdivision of this fraction may yield additional clinical information, as will be shown. One obvious drawback is that not all 17-ketosteroids are androgens, nor are all androgens 17-ketosteroids, so the test is not one for androgens as such. However, it generally parallels the biologic test and is obviously much easier to set up and perform than the latter which involves measuring the growth of a capon's comb.

Since the adrenal cortex is thought to produce androgenic steroids in both men and women, the test is now considered an indication, though not a true measure, of the combined activity of the adrenal cortex and the testes in the male, and, in the female, of the adrenal cortex alone. Since both the adrenal cortex and the testes are under control of the pituitary, the test may be considered to be an indirect measure of the function of that gland. The above concept has been very well presented by Ingram.<sup>2</sup>

### TESTS NOW USED

The following is a general review of what is being done in this field at the present time, and some of the tests that are being carried out in various laboratories are described. It will be noted that most are biological assays, but it is the belief of the author that the increased availability of the chemical test for 17-ketosteroids has stimulated more general investigation and the use of many of the other tests.

*Follicle Stimulating Hormone (FSH).* This pituitary gonadotropin has also been known as prolan A, thy lakentrin and pituitary gonadotropin A. A method for assay was first described by Zondek<sup>3</sup> in 1930 and has more recently been reviewed and modified by Klinefelter, Albright and Griswold.<sup>4</sup> In their method the hormone is precipitated from the urine with alcohol, washed with alcohol and ether, dried in a desiccator, diluted with distilled water and then injected subcutaneously into immature female white mice for three days. The result is considered positive when the uterus is enlarged (to over 7 mg.). After dilutions and calculations they found normal men and women to excrete from 6.6 to 53 mouse units per 24 hours.

A method using rats is preferred by some workers and a recent publication on this subject by Jungck, Maddock and Heller<sup>5</sup> also reports the advantages of ultra-filtration over the alcohol-precipitation dialysis in preparing the urine concentrate for injection. They report that this modification makes the test less complex, less time-consuming and less expensive. The urine concentrate is injected into female rats once every 12 hours for six injections. Twenty-four hours after the last injection the uterus and ovaries are removed and weighed, and the weights recorded as end-points.



The first method using mice and recording results in mouse units seems to be most generally used at present. It is claimed to have the advantage of a more definite end-point. If a high concentration of FSH is present, the modification (using mouse units) of Smith, Albright and Dodge<sup>6</sup> is widely used.

It should be kept in mind that if a woman is menstruating regularly her gonadotropins will be normal, and there will be no need to run this test to ascertain any possible high or low levels.

Various other pituitary hormones can be assayed in urine. These include:

*Interstitial-cell stimulating hormone*—also called luteinizing hormone or metakentrin (ICSH, LH). This is tested for in hypophysectomized rats causing, in the female, restoration of the involuted interstitial or "wheel" cells in the ovaries, and in the male, an increase in weight of the ventral prostate (Simpson, Li and Evans, 1942<sup>7</sup> and Greep, Van Dyke and Chow, 1941<sup>8</sup>).

*The lactogenic hormone*—(also known as prolactin, galactin, or mamotropin) can be assayed in pigeons by measuring the effect on the weight of the crop sac (Riddle, Bates, Dykshorn, 1933<sup>9</sup>). A later method reported by Lyons and Page<sup>10</sup> accomplishes the test by intradermal injections over the crop sacs of squabs. It is reported to be more sensitive, and to detect the hormone in doses of 1 microgram.

*The adrenocorticotrophic hormone (ACTH)*—is tested for in hypophysectomized female rats, starting injections 14 days after operation and measuring the amount of repair which takes place in the involuted adrenals. An adrenal maintenance test is also used, starting injections in male rats immediately after the hypophysectomy and noting maintenance of adrenal weight after two weeks of injections (Simpson, Evans and Li, 1943<sup>11</sup>). Another test for the adrenocorticotrophic hormone is based upon the observation by Sayers, Sayers, Liang and Long<sup>12</sup> that its injection into rats and guinea pigs is followed by a prompt fall in adrenal ascorbic acid, and a slower fall in adrenal cholesterol. It is suggested that these changes are associated with the formation and release of the adrenal cortical hormones.

*Thyrotropic hormone*—commonly tested for with the guinea pig in which injections of the hormone will cause doubling in weight of the thyroid (Rowlands and Parkes, 1934<sup>13</sup>). Another method has been suggested by De Robertis, at first alone and later with Del Conte.<sup>14,15</sup> They noted that injections of the thyrotropic hormone caused an increased formation of intracellular colloid droplets in thyroid epithelium. Recording the number of these droplets was suggested as a method of assay and was reported as being extremely sensitive—detecting as little as 0.0002 Junkmann-Schoeller units. At first the rat was used and later, the guinea pig. More recently Dvoskin<sup>16</sup> reported trying this method in the chick, also recording thyroid weight and thyroid-epithelium cell-height. He concluded that this was not

as sensitive as the test using the guinea pig, but pointed out that more direct comparisons were needed.

In general, the tests for thyrotropic hormone are not yet considered to be completely satisfactory.

*Growth hormone*—can be bioassayed by noting the microscopic effect of injections on the width of the epiphyseal cartilage plate in the tibia of the hypophysectomized female rat (Evans et al., 1943<sup>17</sup>). So far this test has only been used with pituitary extracts.\*

*The posterior pituitary hormones*, vasopressin and oxytocin can also be tested for, but the tests are not considered completely reliable or specific. Vasopressin can be measured by the pressor effect in anesthetized dogs, while oxytocin is measured by its effect in causing contractions of an isolated guinea pig uterus suspended in Locke-Ringer solution and attached to a kymograph. In both methods, comparisons are made with a measured amount of standard dried pituitary powder (Kamm, et al.<sup>18</sup>).

It will be noted that nearly all of these are biological assays. They are being done principally in centers where there is particular interest in investigation in endocrinology.

The *pregnancy tests* usually depend upon the increased excretion of chorionic gonadotropin.

The *Aschheim-Zondek* and *Friedman* tests are well known and widely used. The former utilizes immature mice and the latter a rabbit for the test animal.

More recently, Guterman<sup>19, 20</sup> has reported a pregnancy test which measures pregnandiol in the urine, using a color reaction. This can be done in 3 hours and he reports it to be accurate in 90 per cent of the cases tested. Pregnanediol is the excretion product of progesterone and the test is based upon the increased activity of the corpus luteum and later the placenta during pregnancy. Since desoxycorticosterone acetate also gives rise to pregnandiol, adrenal cortical hyperplasia or tumor may give a false reaction. However, Reinhart and Barnes<sup>21</sup> have recently reported an error of 25 per cent in both positive and negative series using this test. Mack and Parks<sup>22</sup> have also used increased pregnandiol excretion as a pregnancy test. They measured the amount of unpurified pregnandiol that could be precipitated from the urine.

Other tests can be mentioned, such as that using the *South African clawed frog* (*Xenopus laevis*), originally described by Shapiro and Zwarenstein.<sup>23</sup> This depends upon the extrusion of ova within 24 hours after injection of pregnancy urine extracts into the dorsal lymph sac of the female. Another method uses the *male toad* (*Bufo arenarum* Hensel). It has been described by Galli-Mainini of Buenos Aires.<sup>24</sup> In this test 10 c.c. of urine is injected into the lateral lymph sac of the toad. Three hours later urine is collected from the toad by introducing a pipette into the anal canal. A drop is ex-

\* Recently Kinsell et al.,<sup>24</sup> in a communication now in press, reported measurement of growth hormone in plasma by this method.

amined under the microscope and if spermatozoa are present, the test is positive. An accuracy of 95 per cent is reported and it is considered rapid and economical. The same toad can be used again after an interval of one week. The test is widely used in South America. In a more recent communication from this country, Robbins and Parker<sup>25</sup> report the use of the male North American frog (*Rana pipiens*), in a similar manner.

*Adrenal cortical hormones* also appear in the urine and many steroids have been isolated (Dorfman and co-workers, and Browne and co-workers—references given in Jr. Clin. Endocrin., Editorial<sup>26</sup>). One particularly active group of compounds are those with an oxygen atom at C11 on the steroid skeleton.

A *biological test* for the cortical hormones having a glycogenic action was described by Venning, Kazmin and Bell<sup>27</sup> in 1946. It is based upon the fact that the adrenalectomized animal does not deposit glycogen in the liver. The authors measured the effect of 11-dehydro-17-hydroxy-corticosterone, and 11-dehydro-corticosterone and found the former to be three times as active as the latter. The clinical test measures both and is accomplished by extracting a 48-hour specimen of urine. The dried extract is diluted with 10 per cent alcohol in 5 per cent glucose and injected into six to eight male white mice. The mice have been adrenalectomized four days before and given measured concentrations of glucose and saline. Seven injections of the urine extract are given at intervals of 45 minutes and one hour, and an hour after the last, the mice are anesthetized and the livers removed and assayed for glycogen content. The amount of glycogen taken up is in proportion to the glycogenic corticoids in the urine sample. The test has been used considerably in Montreal and Venning and Browne<sup>28</sup> have reported that the normal male excretes 40 to 85 glycogenic units per 24 hours (average 60) and the normal female excretes 25 to 55 glycogenic units per 24 hours (average 39). In Addison's disease and panhypopituitarism they reported the values to be low or not detectable; in anorexia nervosa the values were normal or slightly low; in simple hirsutism the values were normal. However, there was a marked increase in three out of four cases of Cushing's syndrome (males 386 and 42—females 340 and 137 Gl. u./24 hours). The authors felt that in the one instance with a normal value, the disease was in an arrested state. Four cases of acromegaly were tested. Three chronic cases were normal and one recent active case in a male showed a high level (134 Gl. units). Values did not always parallel the 17-ketosteroids.

Later studies by Venning and Browne<sup>29</sup> showed that therapy with testosterone propionate and methyl testosterone generally caused a reduction in the excreted glycogenic corticoids. In the same group of cases, the 17-ketosteroids decreased under therapy with methyl testosterone, but not with testosterone propionate.

Results of use of a colorimetric method for measurement of the 11 oxy-corticosteroids has been reported by Talbot, Albright, Saltzman, Zygmuntowicz and Wixom.<sup>30</sup> The method had been previously described by Talbot,

Saltzman, Wixom and Wolfe.<sup>31</sup> The substances measured were thought to correspond to adrenal cortical steroids with a ketone or hydroxyl group at the 11th carbon atom, a two carbon sugar-like ketolic side chain and an hydroxyl group attached to the 17th carbon atom. Five of these 11-oxy compounds could be separated for the assay by their differential solubility in benzene and water.\* They promote sugar metabolism and have been called the "S" hormones. They are probably similar to and roughly parallel to the glycogenic corticoids measured biologically by Venning and Browne in the test described above.

The results reported on 24-hour urines showed values in normal individuals of both sexes to be from 0.1 to 0.44 mg. per day, with an average of 0.22 mg. In 17 patients with hypoadrenocorticism the output was slightly lower, ranging from 0.02 mg. to 0.29 mg. per 24 hours with an average of 0.14 mg. Two patients with myxedema had low values (below 0.1 mg.). In one case, this rose to normal under treatment with thyroid. They reported that in panhypopituitarism the value was under 0.18 mg. in six out of seven cases. Five cases of adrenal virilism with high 17-ketosteroids were studied and the values for 11-oxycorticosteroids were normal or only slightly elevated. Excretion was studied in 12 patients with Cushing's syndrome and the values were high (0.6 to 12.0 mg. per 24 hours). The values were reduced in two of the patients by testosterone therapy. Three other cases in remission showed normal values. Non specific trauma (burns) showed similar high figures. The value fell to normal in one patient three days before death (thus fitting the theory of the adaptation syndrome of Selye).

Urinary excretions of the *estrogens*, alpha estradiol, estrone and estriol have been measured by *biological methods*. One such is that reported by Smith, Smith and Schiller.<sup>33</sup> In this method a 24- or 48-hour urine is subjected to hydrolysis and then extracted to separate the "strong" phenolic fraction containing the estriol and the "weak" phenolic fraction containing the estrone. The actual method of bioassay was described in another paper (Smith, Smith and Pincus<sup>34</sup>) and utilized spayed female rats in a diestrous state. Three injections of the extract were given four hours apart and a vaginal smear taken 48 hours after the first injection. The smear was considered positive if it showed a pre-estrous, full estrous, or post-estrous phase, and the smallest amount causing a positive result in four out of six rats was considered one rat unit. They also tried *colorimetric determinations*, but the fractions showed large over-estimates due to the presence of inactive chromogenic material.

However, a new fluorometric method has appeared which shows promise of greatly simplifying urinary estrogen assays. Jailer<sup>35</sup> outlined a procedure for extraction using H<sub>2</sub>SO<sub>4</sub> and methyl alcohol, then reading the result in a Coleman Photofluorometer at wave lengths of 4360 Å and 3650 Å. He recorded concentrations of estrone, estradiol, and estriol and reported a con-

\* A modification of this test has more recently been reported by Daughaday, Jaffe and Williams.<sup>32</sup>

stant 50 to 60 per cent recovery of known amounts of the substances in recovery experiments. Cohen and Bates<sup>38</sup> have reported a somewhat similar method using  $\text{H}_2\text{SO}_4$  and ethanol, then reading the resulting red color (Kober reaction) in a photometer at a wave length of 5100 Å. The relative simplicity of these methods is extremely appealing and it is hoped that wider experience will evaluate their specificity.

*Pregnandiol*, which is the excretion product of progesterone, can also be measured in the urine. Venning and Browne in 1936<sup>37</sup> isolated it as the water-soluble compound, sodium pregnandiol glucuronide. In 1937 Venning<sup>38</sup> was convinced of its identity and published a detailed method for its measurement. Urine is extracted with butyl alcohol and the residue treated so that a crystalline substance results which can be weighed. It has a melting point of 267 to 271° C. which is specific for sodium pregnandiol glucuronide. Use of a conversion factor (0.597) easily gives the amount of pregnandiol.

A *colorimetric method* for determination of pregnandiol suggested by Guterman<sup>19, 20</sup> has already been discussed above under "pregnancy tests." As noted, there is still some discussion as to its specificity.

The *androgens* can be assayed *biologically* by measuring the effect of injections of material to be tested on the size of a capon's comb. A capon unit is considered the amount which, after six consecutive daily injections, will cause a 20 per cent average increase in the weight or area of the comb (Funk, Harrow and Lejwa, 1929<sup>39, 40</sup> and Tschopp, 1935<sup>41</sup>). Other methods of bioassay involve the effects on chick combs, stimulation of seminal vesicles, prostate and preputial glands in rats and mice, causing growth of a masculine "sword" in a female swordfish, and stimulating the clasping reflex in frogs (Selye<sup>42</sup>).

However, the test that has stimulated the widest interest and is now more generally available is that for 17-ketosteroids previously mentioned. This is a chemical test, depending on the Zimmermann<sup>1</sup> color reaction for its endpoint. While all 17-ketosteroids are not androgens and all androgens are not 17-ketosteroids, the values generally parallel the results of bio-assays for androgens, and accumulated experience has indicated that the test has considerable clinical value. It should be remembered that in men the androgens (and eventually the excreted 17-ketosteroids) originate in both the testes and the adrenal cortices, and in women they apparently come from the adrenal cortices alone.

In 1941 Fraser, Forbes, Albright, Sulkowitch and Reifstein<sup>43</sup> reported a method that has been widely used. They collected 16-hour (two overnight) specimens, but corrected the figures to excretion per 24-hours.\* The

\* Later Pincus<sup>44</sup> showed that night values for 17-ketosteroids were regularly lower than day values, and Forbes et al.<sup>45</sup> in 1947 also noted this, but thought that the lower night levels were more constant. They suggested collecting two overnight specimens in order to estimate the "basal ketosteroid excretion." However, the common practice at present is to estimate the excretion using a 24-hour urine specimen.

specimens were preserved with 10 c.c. of concentrated HCl. Hydrolysis, ether extraction and purification were done by the combined hydrolysis and extraction method of Callow, Callow, Emmens and Stroud.<sup>46</sup> In this, concentrated hydrochloric acid and carbon tetrachloride were added to the urine and boiled for two hours. The carbon tetrachloride was sucked out and the same extraction for two-hour periods was repeated twice more. The carbon tetrachloride was then distilled off and the residue taken up in benzene. This was fractionated by washing twice with sodium bicarbonate solution and then the mixture was freed from phenols by extracting five times with 2N sodium hydroxide. The benzene solution was evaporated to dryness and extracted four to five times with re-distilled ether. It was then filtered through sintered glass and the filtrate evaporated in a stream of nitrogen. The residue was taken up in absolute alcohol and was then suitable for colorimetric assay. This was done using a photoelectric colorimeter following directions previously published by Callow, Callow and Emmens.<sup>47</sup>

The 1941 paper by Fraser et al.<sup>48</sup> submitted the results of over 1500 assays by their method, which they reported as accurate to 10 to 20 per cent (1 to 2 mg. of sterone per 24 hours). Their normal ranges of total neutral 17-ketosteroids for adult males varied from 8.1 to 22.6 mg. per 24 hours with an average of 13.8 mg., and in adult females, the range was from 5.1 to 14.2 mg. with the average of 9.0 mg. per 24 hours. The values were lowered in old age and also in malnutrition, anemia, infection, and especially in liver disease. In five female patients with Addison's disease, the assays approximated zero, as they did in 15 cases of panhypopituitarism. High assays were present in patients with adrenal tumor or hyperplasia. Cushing's syndrome with adrenal tumor also showed high values. Three patients without tumors showed high or high normal assays. One patient with arrhenoblastoma and one with disgerminoma showed normal levels. Male eunuchoidism and hypothyroidism showed low levels. They noted that about 50 per cent of testosterone propionate injected was recoverable in the urine as 17-ketosteroids.\*

In a review on the subject in 1942, Talbot and Butler<sup>52</sup> concluded that the test did provide diagnostic information and was particularly helpful in detecting hyper- and hypofunction of the adrenal cortex, and hypofunction of the thyroid and pituitary glands.

Many modifications of the test have appeared and are still appearing e.g.

\* Before this time, Callow, Callow and Emmens in 1939<sup>48</sup> had noted that testosterone propionate in doses of 50 mg. per week and up caused an increase in the urinary 17-ketosteroids. Later, Frame, Fleischmann and Wilkins<sup>49</sup> reported that both testosterone propionate and unesterified testosterone caused such an increase, while methyl testosterone did not. Reifstein, et al. in 1945<sup>50</sup> also noted the increase following administration of testosterone propionate and reported that following methyl testosterone there was an actual depression of 17-ketosteroid output in normal patients, and also in patients with Cushing's syndrome and adrenal hyperplasia. Cuyler et al. in 1942<sup>51</sup> reported that the administration of desoxycorticosterone acetate did not cause any constant alteration in 17-ketosteroid output in normal adults.

a more rapid method of extraction by refluxing for 10 minutes with boiling  $\text{CCl}_4$  was suggested by Robbie and Gibson<sup>53</sup> in 1943 and was reported to show a variation of  $\pm 10$  per cent or less. Wooster<sup>54</sup> also presented a simplified method and compared some of the previously reported technics. Another publication comparing previous methods appeared in 1943 by Nathanson and Wilson.<sup>55</sup> They stressed the importance of the adjustment of reading times in the color reaction to make for closer agreement between the various methods. Friedgood, Taylor and Wright<sup>56</sup> compared methods of extraction and hydrolysis and concluded that ether-toluol extraction was superior to that with  $\text{CCl}_4$ .

The most recent rapid method appeared in 1947, reported by Drekter, Pearson, Bartczak and McGavack.<sup>57</sup> They reported that their method could be done in three hours and could easily be adapted to small volumes of urine.

The end-point for the above methods is the total neutral 17-ketosteroids and this is as far as most laboratories carry the test for clinical purposes.

However, other investigators have devised methods to further sub-divide the ketosteroids in the hope of eliciting variations in concentration of individual compounds, or groups of compounds, which might have some clinical importance. Talbot, Berman, MacLachlan and Wolfe<sup>58</sup> used Girard's reagent "T" to separate the ketonic and non-ketonic fractions of the neutral steroids. They found the non-ketonic fraction to contain pregnandiol. The ketonic fraction was then divided into alcoholic and non-alcoholic partitions and the alcoholic portion further divided into alpha and beta fractions with digitonin.

Werner<sup>59</sup> has reported that the non-ketonic fraction contains 10 to 15 per cent of the 17-ketosteroids and that this proportion is fairly constant.

The alpha and beta separation with digitonin was published by Baumann and Metzger in 1940.<sup>60</sup> They found that the beta fraction which precipitates with digitonin was usually 5 per cent or less, though it could be up to 15 per cent in men between the ages of 20 and 27. However, in one case of adrenal cortical carcinoma it was increased to 40 per cent of a total 17-ketosteroid assay of 350 mg. Salter, Cahen and Sappington<sup>61</sup> reported further on this in 1946, and noted that the normal daily averages for the fractions were as follows: male adults—alpha 12.9 mg.; beta 1.3 mg.; female adults—alpha 6.3 mg.; beta 1.3 mg. The ratio of alpha to beta was reported as 9:1 in normals, while in eunuchoidism it was 2:1, in virilism without tumor 3:1, and in virilism with tumor 1:2. The elevation of the beta fraction in adrenal cortical carcinoma was therefore particularly striking. They also noted that the proportion of the beta fraction might be high, even without elevation of the total 17-ketosteroids, in amenorrhea with virilism.

In a review of the subject in 1943, Pincus<sup>62</sup> listed the following as the principal urinary 17-ketosteroids with some of their characteristics:

(1) *Estrone*—eliminated in removing the phenolic fraction by treating with strong alkali during the extraction.

(2) *Androsterone*—alcoholic alpha ketosteroid—0.1 mg. equals 1 international unit of androgenic activity. Probably from testosterone.

(3) *Etiocolanol—3 alpha—17—one*; alcoholic alpha ketosteroid—inactive biologically. Probably from testosterone.

(4) *Isoandrosterone*—alcoholic beta ketosteroid, 0.1 mg. equals 0.12 international units androgenic activity.

(5) *Dehydroisoandrosterone*—alcoholic beta ketosteroid, 0.1 mg. equals 0.33 international units androgenic activity. Probably from the adrenal. (This is more available and is now being used most frequently as a standard for colorimetric comparison.)

(6) *Androsterone 17*—non-alcoholic 17-ketosteroid, 0.1 mg. equals 0.8 international units androgenic activity.

(7) *Delta*<sup>3,5</sup> *androstadienone*—non-alcoholic 17-ketosteroid.

A new chromatographic-colorimetric method of fractionation has been reported by Dingemans, Veld and de Laat.<sup>63</sup> In this method, after some preliminary chemical purification of the urine, the extract is dissolved in carbon tetrachloride, benzene or ethanol. It is then passed through a standardized column of  $Al_2O_3$ . The eluate is withdrawn in several fractions, and the 17-ketosteroids measured separately. They were able to separate eight fractions, starting with only 500 c.c. of urine.

This method is now being used considerably in research starting with large volumes of urine. Recently Lieberman, Dobriner, Hill, Fieser and Rhoads<sup>64</sup> reported analyses of ketonic fractions that had been separated into alphahydroxy (not precipitated by digitonin) and beta hydroxy (precipitated by digitonin) groups. They encountered 35 different substances in the alpha group and seven compounds in the beta group. The individual compounds were identified by infra-red spectrophotometry. Of the 35 alpha-ketosteroids, they reported complete identification of 22 of the compounds and incomplete identification of 13 (nine by melting points alone and four by melting points and C & H analyses). In the group of seven beta-ketosteroids, four were completely identified and three partially identified (one by melting point alone and two by melting points and C & H analyses). The completely identified 17-ketosteroids are listed in table 1.

It should be restated that the above represents late experimental work which is of a fundamental nature. The importance will have to be evaluated when wider experience is reported. However, some of these compounds apparently are found only in certain disease states.

Separation of steroids by paper partition chromatography has recently been reported by Burton, Zaffaroni and Keutmann.<sup>65</sup> While clinical studies using this method of fractionating 17-ketosteroids in urine or other biological material have not yet been reported, the method offers great promise. Attempts to adapt the procedure for clinical use are now in progress (Arrick, M., Gordan, G. S., and Elliott, H. W.—personal communication).



TABLE I

Urinary alpha 17-ketosteroids after Lieberman, Dobriner, Hill, Fieser and Rhoads—1948<sup>64</sup>

- |  |   |
|--|---|
| 1. delta 3,5-Androstadienone-17                                  | 12. Allopregnanol-3 alpha-one-20                    |
| 2. delta <sup>2(or 3)</sup> -Androstenone-17                     | 13. Pregnanol-3 alpha-one-20                        |
| 3. 3-Chloro-delta <sup>5</sup> -androstenone-17                  | 14. Androsterone                                    |
| 4. Etiocholanol-3 alpha-one-17 acetate-3                         | 15. delta <sup>9</sup> -Androstenol-3 alpha-one-17  |
| 5. delta <sup>11</sup> (?) -Androstenol-3 alpha-one-17 acetate-3 | 16. 17-Isopregnanol-3 alpha-one-20                  |
| 6. Androsterone acetate  | 17. delta <sup>9</sup> -Etiocholenol-3 alpha-one-17 |
| 7. Allopregnanedione-3,20  | 18. Etiocholanol-3 alpha-one-17                     |
| 8. Pregnanedione-3,20  | 19. Androstanediol-3 alpha, 11 beta-one-17          |
| 9. Androstanedione-3,17  | 20. Etiocholanol-3 alpha-dione-11,17                |
| 10. Etiocholanedione-3,17  | 21. Pregnanediol-3 alpha, one-20                    |
| 11. delta <sup>4</sup> -Androstenedione-3,17                     | 22. Allopregnanediol-3 alpha, 6-one-20              |

## Urinary beta 17-ketosteroids

1. delta<sup>2(or 3)</sup>-Allopregnenone-20
2. Allopregnanol-3 beta-one-20
3. Allopregnanol-3 beta-one-20
4. Dehydroisoandrosterone
4. Isoandrosterone

## TESTS GENERALLY AVAILABLE

As noted before, many of the tests described above are being performed only in centers where research in endocrinology is in progress. However, some are available away from such centers, and such availability seems to be increasing.

Perhaps the most widely used are the pregnancy tests, with the Aschheim-Zondek and the Friedman tests being the most frequent. It should be recalled that these are also positive in patients with chorionepithelioma and in hydatidiform mole. The Galli-Mainini (toad) test<sup>24</sup> has been reported to be in general use in South America. The Guterman colorimetric test<sup>19, 20</sup> for pregnandiol has not yet been generally accepted and is still the subject of some difference of opinion.<sup>21</sup>

The test for total neutral 17-ketosteroids<sup>43</sup> is probably the next most widely performed. It gives a colorimetric end-point and has become accepted as an index though not a true measure of androgen activity in the individual. The biological test using capons is still being used in some centers, and of course, remains the true test for androgens.

The *follicle-stimulating pituitary gonadotropins* (FSH) are now being more generally measured, with the method using mouse units<sup>4</sup> the most widely accepted procedure.

Tests for pregnandiol<sup>10, 38</sup> are being carried out in many centers, especially where there is much work in obstetrics and gynecology. It will be recalled that pregnandiol is principally the excretion product of progesterone.

The fluorometric test for estrogens<sup>35, 39</sup> while not yet in wide use, shows promise of being a relatively simple method.

Glycogenic corticoids from the adrenals have been measured extensively clinically but not in many centers. It will be recalled that this is a biological test which requires adrenalectomized mice.<sup>27</sup> The colorimetric test for 11-

oxycorticosteroids<sup>30</sup> has also had clinical trial but in a limited number of centers. Elevation of values seems most marked in Cushing's syndrome and they are reported to drop to normal levels if the disease becomes inactive.

#### EXPERIENCE AT THE UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

Tests for 17-ketosteroids and for follicle-stimulating hormone have been available at the University of California Hospital for the past three and a half years.\* The Hormone Laboratory was set up and organized by Doctor Nellie Halliday, and started to function in September, 1944. At first only tests for 17-ketosteroids were available but soon the bioassay for FSH was set up. Dr. Halliday supervised the laboratory and trained all technical help until December, 1946. Since then, the tests for 17-ketosteroids have been run in the laboratory of Dr. Gerson Biskind and tests for FSH have been performed in the Endocrine Laboratory of the Department of Obstetrics and Gynecology under the supervision of Dr. Allan Palmer.

#### METHODS—17-KETOSTEROIDS

Under Dr. Halliday the urines were extracted by the method of Pincus<sup>66</sup> using the Zimmermann reaction which is summarized in table 2.<sup>66, 67</sup> The separation was carried to the ketonic fraction which, it will be remembered, represents 85 to 90 per cent of the total neutral 17-ketosteroids in fairly constant proportion.† The colorimetric estimation of end-points was performed according to the method of Holtorff and Koch<sup>68</sup> using the Klett-Summerson photoelectric colorimeter connected through a G-E voltage stabilizer. It is of interest that Nathanson and Wilson<sup>65</sup> compared several methods of colorimetric estimation and preferred this one because of less technical difficulty and smaller error.

In Dr. Halliday's experience, the normal ranges were as follows:

*Women* over 16 years (36 cases): 5.5 to 11.4 mg. per 24 hours  
Ketonic, with an average of 8.7 mg.  $\pm$  1.6 mg.  
*Men* over 16 years (16 cases): 10.7 to 20.6 mg. per 24 hours  
Ketonic, with an average of 14.7 mg.  $\pm$  3.0 mg.

The convenient fraction of 10 per cent was added to these figures in order to make them comparable with the figures of other authors whose results are reported as the total neutral fraction. This comparison with normal ranges noted by several other authors is made in table 3.

\* The laboratory was started under the leadership of Dr. H. Lisser with the assistance of Dr. Evelyn Anderson, Department of Medicine; Dr. Francis S. Smyth and Dr. William C. Deamer, Department of Pediatrics; and Dr. Robert A. Lyon, Department of Obstetrics and Gynecology. The organization and maintenance were aided by generous contributions from the Ciba Pharmaceutical Company and from the Christine Breon Fund for Medical Research as granted by the Research Committee under the chairmanship of Dr. Theodore L. Althausen.  
† However, in some instances, Dr. Halliday found the non-ketonic fraction to comprise as much as 25 per cent of the total.

TABLE II  
Flow Chart for Extraction of 17-Ketosteroids from Urine

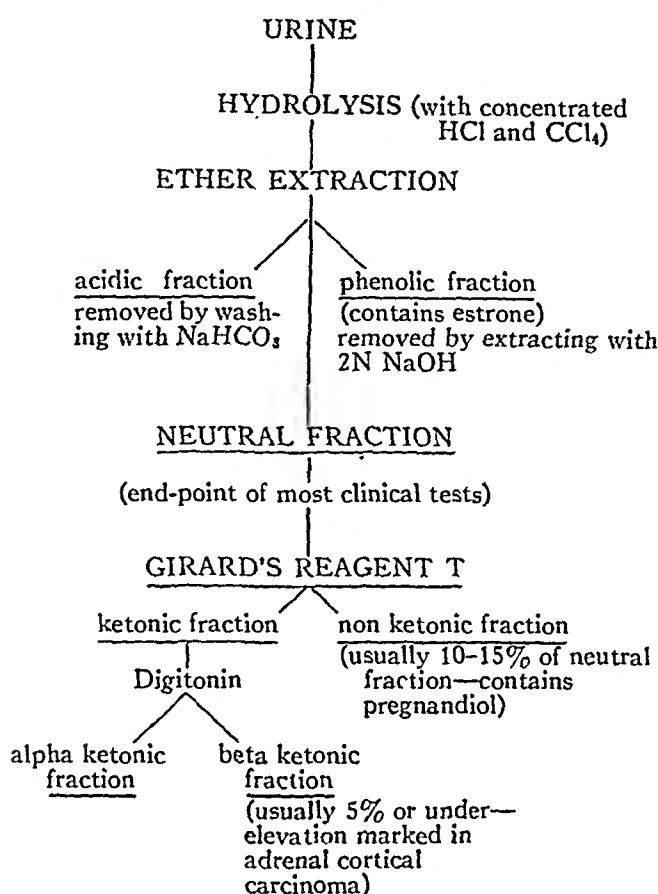


TABLE III  
Comparison of Normal Values for Total Neutral 17-Ketosteroids as Mg. per 24 Hrs.  
from Different Laboratories

Author	Females			Males		
	Lower	Upper	Average	Lower	Upper	Average
Univ. of Calif., Dr. N. Halliday	6.0 mg.	12.5 mg.	9.6±1.8 mg.	11.8 mg.	22.7 mg.	15.2±3.3 mg.
Callow et al., 1939 <sup>46</sup>	1.7 mg.	12.6 mg.	6.75 mg.	3.5 mg.	15.0 mg.	9.05 mg.
Fraser et al., 1941 <sup>43</sup>	5.1 mg.	14.2 mg.	9.0 mg.	8.1 mg.	22.6 mg.	13.8 mg.
Talbot et al., 1943 <sup>69</sup>	2.8 mg.	9.2 mg.	6.8 mg.	8.8 mg.	15.6 mg.	11.0 mg.
Luft, 1943 <sup>78</sup> (from Sweden)	12.4 mg.	23.1 mg.		14.3 mg.	43.1 mg.	
Hoffman, 1944 <sup>70</sup>	5 mg.	18 mg.	10 mg.	7 mg.	27 mg.	15 mg.
Venning and Browne, 1947 <sup>23</sup>	7 mg.	18 mg.	11 mg.	10 mg.	25 mg.	17 mg.
Forbes et al., 1947 <sup>45</sup>	3.8 mg.	16.9 mg.	8.2 mg.	6.7 mg.	27.2 mg.	12.5 mg.

*Ranges for children* (boys and girls) were taken from Talbot et al.<sup>60</sup> and were as follows:

Up to 3 years—none.

At 8 years—0 to 2.0 mg. per 24 hours total neutral, with an average of 0.95 mg.

At 12 years—1.5 to 5.0 mg. per 24 hours total neutral, with an average of 3.4 mg.

At 16 years—4.0 to 9.5 mg. per 24 hours total neutral, with an average of 7.2 mg.

They noted that in general the values approximate 0 under the age of 10, and should be at least 1 mg. by the age of 12. The adrenal cortex was thought to be the chief source of 17-ketosteroids during childhood.

Dr. Biskind used a method slightly modified from that of Robbie and Gibson<sup>58</sup> and reported values as total neutral 17-ketosteroids. He did not proceed beyond this step to separation of the ketonic fraction.

In appraising the results expressed below, the normal diurnal variation must also be considered. It was reported by Werner<sup>59</sup> that daily total neutral 17-ketosteroids fluctuated from 6 mg. to 14.2 mg. and from 10.1 to 17.3 mg. in two normal males, while in one female the fluctuation was from 6.9 to 12.2 mg. per 24 hours. However, Forbes and co-workers<sup>45</sup> in 1947 felt that although there was wide variation in the normal range, repeated estimations on the same individual showed considerable consistency. They also noted that after any medical or surgical injury, the excretion would rise for one to three days and then fall to below the usual normal level—returning gradually to normal as convalescence was achieved. Dingemanse et al.<sup>63</sup> reported from Holland that the 17-ketosteroid excretion was higher in post-war normal urine specimens than in those collected during the war, and suggested that the inadequate or unbalanced diet that prevailed for many years there during occupation had been a factor in depressing the values.

*The FSH method* used by Dr. Halliday was a slight modification of the test of Klinefelter, Albright and Griswold<sup>4</sup> which has been described above in the section on "Tests Now Used." The chief modification was the difference in adjustment of volumes so that several levels could be tested on the same urine specimen. She found normal patients to be in the following ranges:

*Adult men and women* (non-menopausal) 6 to 50 mouse units per 24 hours.

*Children:* very low.

Dr. Palmer also used the method of Klinefelter, Albright and Griswold, considering a positive reaction a 50 per cent or more increase in weight of the uterus. The ovaries were also examined histologically to rule out any possible estrogenic effect in causing the increase in uterine size. In his experience the normal range in adult men and women (non-menopausal) varied from 5 to 40 mouse units per 24 hours.

## RESULTS

Four hundred and eighty-eight estimations of 17-ketosteroids and 233 estimations of FSH are available for this report.\* The results are listed under diagnoses.

In all instances 10 per cent was added to the figures for ketonic fraction in order to make them comparable with those for the total neutral fractions. This convenient percentage seems permissible considering the variations in the test, in the daily output, and in the range of normal values.

## ACROMEGALY

17-Ketosteroids were estimated in 14 cases. The 24-hour value for total neutral fraction varied from 4.9 mg. (in a female patient aged 60 with diabetes) to 25.5 mg. (in a male patient aged 58 with clinical evidence of moderate activity). The average value of the five male patients was 23.4 mg. per 24 hours and of nine female patients, 11.2 mg. per 24 hours. Thus the male patients were slightly high, being on the average above the normal range, and the female patients were generally higher than average, but within the range of normal.

Fraser et al.<sup>48</sup> in 1941 reported one male patient with a level slightly below the normal range and five females, three with levels below normal and two with levels in the upper limits of normal. In 1943 Klinefelter et al.<sup>4</sup> reported on three males—one was under normal, one was low average and one slightly over normal. There were also seven female acromegalics, of whom three showed slightly low levels (the lowest having diabetes), three normal levels and one slightly high. Hoffman in 1944<sup>70</sup> reported on six patients, three of whom were low and three normal. In 1947 Venning and Browne<sup>28</sup> reported two males with values slightly above normal and two females with levels within the upper limits of normal.

FSH was determined nine times in eight patients. The excretion was within normal range in six patients, definitely above normal in one, and at least normal in another. Of the last two, one patient was a female, aged 34 whose urine showed a positive test for 94 mouse units per 24 hours and a negative test for 140 mouse units. The other case was in a male of 24 with active acromegaly who showed a positive test at 30 mouse units, which was the highest level tested.

Klinefelter et al.<sup>4</sup> in 1943 reported on FSH in acromegalics. Seven were low, two normal and one was high. The latter was a female aged 40 who had passed the menopause.

\* Patients tested have been from all departments of the University of California Hospital and Clinic and comprise both private and clinic cases, including those of Dr. Leela S. Craig, Dr. L. E. Curtis, Dr. W. C. Deamer, Dr. M. B. Goldberg, Dr. G. S. Gordan, Dr. L. W. Kinsell, Dr. H. Lisser and Dr. R. Perlman. The data are available as a result of the team work and generosity of all the above. Future publications by members of this group will undoubtedly present some of the work in greater detail.

## SIMMONDS' DISEASE

Nine patients with this diagnosis were tested 14 times for 17-ketosteroid output. One instance was in a boy aged 12 who also had diabetes insipidus. His level was 3.2 mg. total per 24 hours. The rest were adults of whom four were males and four were females. The ranges in the males varied from 1.1 mg. to 4.7 mg. per 24 hours with an average of 2.7 mg. total neutral per 24 hours.

In the four female patients, the variation was between 1.8 mg. and 4.0 mg. with an average of 2.7 mg. total neutral per 24 hours.

Thus in the younger patient, the value was within normal limits, but below the average, while in the adults the values were below the normal range in all cases, with the averages of sexes equal, and therefore being especially low for the male patients.

This differs with some of the earlier reports in the literature. Fraser et al.<sup>43</sup> in 1941 reported nine cases with values in eight being under 0.5 mg. per 24 hours. Hoffman<sup>70</sup> in 1944 reported 15 patients, with only one showing an excretion of over 1 mg. Klinefelter et al.<sup>4</sup> in 1943 also reported very low values, mostly under 0.5 mg. Slightly higher values were reported by Talbot et al.<sup>80</sup> in 1947 with levels of 1.4 and 1.6 mg. in two patients, and Venning and Browne in 1947<sup>28</sup> reported five adults with values up to 3.5 and 4.2 mg. though all were definitely below the normal range.

*FSH* was tested 15 times in eight patients. In the patient mentioned above (a boy aged 12), the test was positive at 4 mouse units and negative at 11 mouse units per 24 hours. Of the remainder, negative tests were reported at 7.2, 9.0, 6.7, 6.4, 3.0, 2.9, 5.5, 2.8, 7.1 and 3.2 mouse units per 24 hours, indicating that the patient's output was under these levels. However, positive tests were reported at 8.0, 3.8, 20, and 8.1 mouse units per 24 hours. The high level was in a patient where two previous tests had shown (1) positive results at 8 mouse units and negative at 23 mouse units, and (2) negative at 7.2 mouse units per 24 hours. She had had diabetes before the onset of her disease which followed a pregnancy and had then developed the Houssay phenomenon with marked amelioration of the severity of the diabetes and extreme sensitivity to insulin.

Klinefelter, et al.<sup>4</sup> in 1943 reported low levels in 10 cases. Two had positive tests at 3 mouse units and negative tests at 6.6 mouse units. One doubtful case was positive at 6.6 mouse units. All the rest were negative at levels of 3 and 6.6 mouse units per 24 hours.

## ANOREXIA NERVOSA

*17-Ketosteroids* were measured 16 times in 12 patients with this diagnosis. All were adults and all but one were in females. The only male, a man of 49, showed a level of 1.8 mg. total per 24 hours—lower than any of the male patients in this series with true Simmonds' disease. The 11 female patients varied from 1.5 mg. to 14.8 mg. with an average of 7.3 mg. total neutral per 24 hours. Thus although the average of these patients was

within the normal range, it must be pointed out that there is overlapping with the values found in the patients with Simmonds' disease. Individual values of 1.8, 2.1 and 1.5 mg. per 24 hours in anorexia nervosa are lower than those of 3.1, 2.2, 4.7, 3.9 and 3.2 which were found in the patients with Simmonds' disease and indicated that, in our experience, the test is not always helpful in deciding whether an individual case is one of anorexia nervosa or Simmonds' disease.

Fraser et al.<sup>43</sup> in 1941 reported mostly low normal values, but levels as low as 1.7, 2.4, and 3.6 mg. were included. Klinefelter et al.<sup>4</sup> in 1943 reported a similar spread in five patients with low values such as 1.2, 1.8 and 1.9 being included. In 1947 Venning and Browne<sup>28</sup> reported low (3.5 to 4.0 mg.) and low normal figures in three patients, and Sunderman and Rose<sup>71</sup> in 1948 reported a patient, a female of 28, with a value of 2.3 mg. per 24 hours for 17-ketosteroid excretion. Landau, et al.<sup>72</sup> in 1948 reported that 17-ketosteroid excretion was cut in half by four days of starvation.

*FSH* was tested in eight patients a total of 10 times, all of whom were adult females. Four showed negative results at levels of 8.5, 8.0, 4.2 and 48.6 mouse units per 24 hours. Positive results were reported at 17.9, 45, 6.7, and 5 mouse units per 24 hours. Two patients showed doubtful positive results (one animal positive and one negative) at levels of 32 and 136 mouse units per 24 hours. Thus most were within normal range. In one patient, a typical instance in a female aged 27, three urine specimens were reported as showing the following values:

1. Positive at 6.7, negative at 40.2, m.u./24 hours.
2. negative at 4.2, m.u./24 hours.
3. Plus-minus at 32, m.u./24 hours.

showing how the results of the test can vary in the same patient.

Klinefelter et al.<sup>4</sup> in 1943 reported normal values in five patients while Sunderman and Rose in 1948<sup>71</sup> reported an *FSH* of 0. in their patient.

### HYPOPHYSEAL INFANTILISM

*17-Ketosteroids* were determined 25 times in 22 cases with this diagnosis. One patient, a boy aged four and one-half, was within normal range for his age with a value of 1.6 mg. per 24 hours.

Six patients aged 8 to 11 ranged in excretion from 0.6 to 11.9 mg. with an average of 3.9 mg. per 24 hours. This is slightly above the normal average for that age. The patient with the high level was a girl aged nine with a craniopharyngioma.

In the group from 12 to 15 years, there were seven patients. Values ranged from 1.0 to 6.2 mg. total neutral, with an average of 4.0 mg. per 24 hours. This was at the lower limit of the normal range, and definitely below the normal average.

Males of adult age in this group numbered six and their values ranged from 1.2 to 5.9 mg. with an average of 3.5 mg. total neutral per 24 hours. This is, of course, well below the normal range.

Two adult females showed values of 0.7 mg. and 1.1 mg. with an average of 0.9 mg. per 24 hours.

Thus in our experience with patients with hypophyseal infantilism, the 17-ketosteroids were normal until the age of 12, low normal up to 16, and definitely below normal once adult age has been reached, especially in females.

In 1941, Fraser et al.<sup>43</sup> reported seven patients, all with values under 0.5 mg. Then in 1943, Klinefelter, et al.<sup>4</sup> reported five patients, all low, with three showing values under 0.5 mg. Talbot et al.<sup>69</sup> reported nine cases with an average age of twelve and one-fourth years—all with low levels. Engstrom and Mason<sup>73</sup> in 1944 reported a boy of 18 with low levels (0.4 to 0.8 mg. per 24 hours). In 1947, Talbot et al.<sup>30</sup> reported three adults with low levels, but Venning and Browne<sup>28</sup> reported a girl of two and one-half with a slightly high level (3.2 mg. per 24 hours).

*FSH*—21 estimations were reported on 18 patients. *Negative* tests for patients under 16 years of age were obtained at levels of 3.7, 12.8, 6.0, 10.1, and 4.8 mouse units per 24 hours. These were the lowest levels tested in these cases. *Positive* results in patients in this age group were reported at 4.2, 3.9, 3.0, 24.6, 8.0 and 5.0 mouse units per 24 hours and *doubtful positive* tests at 34, 8.2, and 33.6 mouse units per 24 hours (one animal positive, the other negative). Of the six patients of adult age, four showed negative values at (1) 7.3 and 5.2; (2) 6.4; (3) 6.4, and (4) 11.6 mouse units per 24 hours, lowest levels tested, and two patients had positive values at 5.9 and 8.7 mouse units per 24 hours.

From this, one must conclude that the *FSH* in hypophyseal infantilism is usually within normal range, though most frequently in the lower levels. Occasionally it is below normal levels.

Klinefelter et al.<sup>4</sup> in 1943 reported low levels in five patients.

#### PITUITARY MALFUNCTION OR HYPOPITUITARISM

Eleven tests were run for 17-ketosteroids on 11 patients so labelled. Six were in the age group, 12 to 15, and showed values ranging from 1.2 mg. to 16.4 mg. with an average of 7.1 mg. total neutral per 24 hours. The highest level was in a boy aged 14 who had diabetes insipidus.

One male adult was in the series and showed a level of 18.1 mg. total per 24 hours. He was a man of 58 who had scant sexual hair and atrophic testes.

The four adult female patients ranged from 4.3 mg. to 8.4 mg. with an average of 6.9 mg. total neutral per 24 hours—slightly below the normal average.

Fraser et al.<sup>43</sup> in 1941 reported two patients with pituitary tumors. The level of excretion in one was low, and in the other, it was normal. Talbot et al.<sup>30</sup> and Venning and Browne<sup>28</sup> each reported patients with pituitary tumors who showed slightly low levels of 17-ketosteroids.



*FSH* tests in this group totalled five. One in a boy 15 years of age was under 6.7 mouse units per 24 hours. The other four in adult females were within normal limits. One interesting patient, a woman of 35, had developed a carcinoma of the nasopharynx 11 years before. Following operation, she had been given heavy roentgen therapy to the area, and it is estimated that approximately 4000 r reached the pituitary region. Following this, the patient developed the following symptoms of hypopituitarism: Loss of weight and then inability to gain, severe exhaustion, marked atrophy of breasts, diminution of libido, inability to conceive (two previous normal pregnancies) and change in menstrual function from a regular 28-day cycle with periods of moderate flow lasting three to four days, to an irregular cycle with intervals of one to four months and very scant periods lasting one-half to one day. To the author's surprise, *FSH* level in this patient was positive at 30 mouse units per 24 hours. Repeat tests were (1) positive at 5 m.u. and negative at 80 m.u.; (2) positive at 15 m.u. and negative at 30 m.u. It is difficult to reconcile these results with the clinical picture.

#### HYPERTHYROIDISM

*17-Ketosteroids* were tested seven times in six patients. Two males showed values of 77.3 and 9.7 mg. total neutral, and four females had values of 11.8, 9.2, 8.2, 7.6 and 8.5 mg. total neutral per 24 hours. All were therefore within normal limits except the one male patient with the high level of 77.3 mg. He was reported as having a BMR of + 37 per cent and showing no other reason for the high ketosteroid excretion.

Baumann and Metzger<sup>60</sup> in 1940 reported normal or slightly low levels in five patients and Fraser et al.<sup>48</sup> in 1941 reported low levels in three patients. Engstrom and Mason<sup>73</sup> collected 22 patients with hyperthyroidism and found the values in all to be slightly low. Forbes et al.<sup>45</sup> in 1947 reported on 19 patients, all with slightly low levels. Venning and Browne<sup>28</sup> that same year reported a case with a low normal level.

*FSH* was measured five times in four patients. All were adults and showed the following values:

Male, age 56—positive at 43 mouse units/24 hours.

Male, age 41—positive at 6.9 and negative 51.2 mouse units/24 hours.

Female, age 40— $\pm$  at 64 and negative at 132 mouse units/24 hours.

—positive at 60 and negative at 128 mouse units/24 hours.

Female, age 26—positive at 7.4 and negative at 44.1 mouse units/24 hours.

It can be seen that one patient tended to be slightly high, two were within normal limits and one had a level that was at least normal.

#### HYPOTHYROIDISM

*17-Ketosteroids* were measured once each in 10 patients. Three male patients showed values of 25 mg., 16.4 mg. and 4.8 mg. total neutral per

24 hours. The last case was one of severe myxedema as yet untreated in a man of 67. Seven female patients showed values ranging from 4.2 mg. to 22.9 mg. with an average of 13 mg. total neutral per 24 hours. These figures somewhat exceeded the usual normal range, and in females, therefore, the average was slightly high.

Values have been reported lower than this in the literature. Baumann and Metzger<sup>60</sup> in 1940 reported a value of 3.6 mg. in a female patient aged 40 with myxedema. Fraser et al.<sup>43</sup> in 1941 reported levels as low as 1 mg. or under 0.5 mg. with all values being definitely low. Talbot et al.<sup>69</sup> in 1943 reported low values in 12 children and in 1944, Engstrom and Mason reported<sup>73</sup> low values in 10 patients. Benda and Bixby<sup>74</sup> in 1947 reported low values in three adult cretins and in one hypothyroid.

*FSH* was tested five times in as many cases. The only male was the case of severe myxedema already mentioned and his report was of a positive test at 30 mouse units per 24 hours, so his level was at least that high. The four female patients were all within normal range.

Klinefelter et al.<sup>4</sup> in 1943 reported a normal *FSH* in one patient.

### DIABETES MELLITUS

*17-Ketosteroids* were tested six times in as many patients. One male showed a level of 1.2 mg. per 24 hours. This specimen was collected after an operation for removal of a thyroid nodule. The five female patients were all adults. Three were definitely hirsute and showed levels of 4.7 mg., 13.3 mg. and 9.5 mg. One was a patient with ovarian aplasia and showed a level of 5.2 mg. The last patient, a girl of 16, excreted 6.2 mg. total neutral per 24 hours. Two of these female patients were, therefore, below the usual normal range; but none were above the normal range, even the bearded diabetics.

Fraser et al.<sup>43</sup> in 1941 reported results in four females and two males with diabetes. All but one were slightly below the normal range and that one was below the average normal. Miller and Mason<sup>75</sup> in 1945 studied the excretion in 64 adults and 17 juvenile diabetics. All were below average normal and most were below the normal range. They found no correlation with the severity of the diabetes. In 1946 Salter et al.<sup>61</sup> reported low levels in two patients, though the diabetes was complicated in one case by eunuchoidism, and in the other by Addison's disease. Venning and Browne<sup>28, 29</sup> in 1947 reported four cases in whom the 17-ketosteroid output was normal. That same year, Forbes et al.<sup>45</sup> reported nine females with low outputs, the average being 5.1 mg. and six males with an average output that was even lower at 4.6 mg.

*FSH* was measured in only two cases, with negative results. One in a boy of three was negative at a level of 3.2 mouse units per 24 hours and the other in a girl of 19 was negative at 7.9 mouse units per 24 hours. The latter patient had been a severe juvenile diabetic, was rather short, and was still amenorrheic at that age.

## CUSHING'S SYNDROME

*17-Ketosteroids* were tested 13 times in 11 patients. One was a girl aged 11 whose excretion level was 4 mg. total neutral per 24 hours. Two male adult patients excreted 29.3 mg. and 12 mg. per 24 hours respectively, and in eight females the values ranged from 5.6 mg. to 20.3 mg. with an average of 16.6 mg. total neutral per 24 hours. While this is above the usual normal range, the elevation is not marked.

Fraser et al.<sup>43</sup> in 1941 reported slightly elevated levels in four patients, one with adrenal carcinoma. Another case with adrenal carcinoma was high with an excreted level of 74 mg. per 24 hours. Hoffman<sup>70</sup> in 1944 reported that in cases without adrenal cortical carcinoma the values were normal or slightly high (range 7.5 to 36 mg. per 24 hours), but in five patients with adrenal carcinoma the values were high (range 40 to 288 mg. per 24 hours). Salter et al.<sup>61</sup> in 1946 reported moderately high values in a girl of 12 years (12 mg.) and found the proportion of alpha and beta partitions to be normal. In 1947 Talbot et al.<sup>30</sup> reported eight patients. Two were slightly low, one was normal, three were slightly above the normal range and two were moderately elevated (44 and 51 mg.). Venning and Browne<sup>28, 29</sup> reported seven cases, of which four were normal and three slightly high. Kepler and Mason<sup>70</sup> reported three cases—one was normal and two were slightly high (24 and 28 mg.). Beta fractions were also measured and were 2 per cent and 5 per cent in two of the cases, but in the third patient, a woman aged 27 whose total excretion was 24 mg., the beta fraction was 14 per cent.

*FSH* was tested four times in a like number of patients. All were adults and two were within normal limits. The other two showed higher levels. One, a female of 38, was positive at 51.2 mouse units per 24 hours and doubtfully positive at 96 mouse units. Another female patient of 27 showed a positive reaction at 51 mouse units, but no higher levels were tested.

## ADRENOGENITAL SYNDROME

## (Hyperadrenalism, Pseudohermaphroditism)

*17-Ketosteroids* were estimated 55 times in this group of 48 patients. Two female patients had carcinoma of the adrenal. One, a female, fifteen and a half years old, did not have an elevated level, excreting 6.8 mg. total neutral per 24 hours. The other showed a pre-operative level of 82.1 mg. total neutral per 24 hours and after operation, the output dropped to 6.3 mg. In seven months the level had increased to 19.3 mg. per 24 hours, indicating a possible but not proved recurrence of the tumor. Additional evidence for this conclusion was furnished by the fact that the beta fraction in this patient was 55 per cent pre-operatively, and post-operatively was still at 29 per cent. It will be recalled that the beta fraction is usually under 5 per cent and seems to increase particularly with adrenal cortical carcinoma. The analyses for this fraction were kindly performed for us by Dr. Ralph I. Dorfman.

Seven patients were in the age range three weeks to two years, where

normally no 17-ketosteroids are detected. Eight values were done and ranged from 0.4 mg. to 17.5 mg. with an average of 7.6 mg. total neutral per 24 hours.

In the age group three to seven, there were 13 patients and levels of excretion ranged from 1 mg. to 15.4 mg. with an average of 4.5 mg. total neutral per 24 hours. The highest level was in a boy aged three with the adrenogenital syndrome.

Patients between the ages of eight and 11 numbered 12 and each had one test. The values varied from 2 mg. to 11 mg. with an average of 4.9 mg. total neutral per 24 hours. The highest was in a male aged nine with precocious puberty.

In the group between 12 and 15, there were four patients. Values were 7.1 mg., 8.2 mg., 8.7 mg., and 75.6 mg. total neutral per 24 hours. The latter case was a girl of 12 who had had two previous operations on the adrenals but was still hirsute, with masculine build. At the first operation, half of the left adrenal had been removed and had shown marked hyperplasia, also an adenoma had been removed from the cortex of the right adrenal. Four years later (at the age of nine) the remainder of the left adrenal had been removed and still showed marked hyperplasia.

Only two adult "male" patients were in this group. Both were pseudohermaphrodites. One showed values of 22.7 and 23.1 mg. per 24 hours, but the other aged 24 excreted 166.6 mg. total neutral per 24 hours. This remarkable individual had a short muscular, very masculine body configuration with apparent hypospadias and undescended testes. On exploration, however, ovaries were found. There was no evidence of adrenal tumor.

The remaining eight cases were all adult females and showed values ranging from 10.1 mg. to 95.5 mg. with an average of 28.5 mg. total neutral per 24 hours. The patient with the high level was another instance of adrenal cortical hyperplasia in a girl of 16 in whom one adrenal and a third of the other had been previously removed.\*

There are numerous reports in the literature of patients of this type. In 1940 Baumann and Metzger<sup>60</sup> reported one patient with adrenal carcinoma who showed a low level (2.3 mg.) three weeks after operation, but later, after recurrence of the tumor, excreted 367 mg. per 24 hours of which 111 mg. were in the beta fraction. Fraser et al.<sup>43</sup> in 1941 reported three cases— one girl, aged three and one-half, with an adrenal tumor excreted 176 mg.— three with adrenal hyperplasia were moderately increased, with levels up to 72.4 mg. in a woman of 23. Nathanson and Aub<sup>77</sup> in 1943 reported slight elevation (to 3.5 mg.) in a boy of four and one-half years of age with precocious puberty. That same year, Luft<sup>78</sup> reported on two boys. One aged two and one-half with adrenal hyperplasia excreted up to 52.5 mg. The other, aged seven, who

\* Since the original preparation of the manuscript, an instance of virilism has been seen in a woman aged 63. Increased beard and body hair growth, baldness, amenorrhea, and an enlarged clitoris had gradually developed over a period of 30 years. 17-Ketosteroid excretion was 741 mg. total neutral per 24 hours with a beta fraction of 170 mg. (23 per cent). A large, encapsulated adrenal cortical carcinoma was removed surgically. One week later, the 17-ketosteroid had dropped to 15.8 mg. and one month later, the level was 9.1 mg. total neutral per 24 hours.

had a carcinoma of the adrenal, excreted 155 mg. per 24 hours. In 1944 Engstrom et al.<sup>79</sup> reported eight patients with adrenal tumor—four were moderately increased (up to 54.6 mg. in a girl of 16) and four were markedly increased with the highest level of excretion being 857 mg. in a woman of 45. They also reported three patients with pseudohermaphroditism and adrenal hyperplasia. All showed definite increases, the highest being 75 mg. in a girl of 19. Hoffman<sup>70</sup> reported eight patients with adrenal carcinoma. Two were adults and showed high levels (215 and 367 mg.) and six were children, all of whom were high, with four being over 100 mg. and the highest level at 420 mg. Twenty-two of his patients had adrenal cortical hyperplasia. Five of these were adults and varied from 35 to 52 mg. and 17 were children, with excretions varying from 17.8 to 74 mg. Raices and co-workers<sup>80</sup> in 1945 reported two patients, one with adrenal tumor and the other with hyperplasia. Both had normal 17-ketosteroids. Warren<sup>81</sup> that same year reported four patients with tumor in whom high levels were found (83, 690, 269, and 126 mg.). Two female children aged seven and ten and one-half with virilism showed an excretion level of 158 mg. during a pregnancy. After delivery the level dropped to 23 mg. and later, after removal of an ovarian tumor, to a still lower level of 12.8 mg. Three weeks after birth, the child, who appeared to be a normal male infant, was found to excrete 138 mg. per 24 hours. A study by Salter et al.<sup>81</sup> in 1946 showed normal, moderately elevated and high levels in a series of 10 patients. The highest excretion was 800 mg. and occurred in a patient with adrenal carcinoma. The beta fraction in this case was 222 mg. Herweg et al.<sup>82</sup> in 1946 reported two patients who were feminized males. In both, the 17-ketosteroid excretion was normal. In 1947 Venning and Browne<sup>28</sup> reported moderate increase of 17-ketosteroid excretion in a boy of two and one-half years of age. Talbot et al.<sup>30</sup> reported moderate elevation in five patients with adrenal cortical hyperplasia, and marked elevation to 830 mg. in one patient with adrenal carcinoma. Kepler and Mason<sup>76</sup> reported six patients with adrenal tumor. One patient showed normal excretion, two others showed moderate increase and the remaining three were high, with the top level being 1005 mg. in a woman of 55. The beta fraction in that patient was 77 per cent. Two patients with hyperplasia showed levels of 31 mg. in a girl aged 10 and 123 mg. in an adult. The beta fractions in these cases were 14 and 20 per cent. These authors concluded that values of over 50 mg. with a beta fraction of over 50 per cent were strong evidence in favor of an adrenal carcinoma. In 1948 Dobriner et al.<sup>87</sup> reported two patients with hyperplasia who showed 17-ketosteroid levels of 62 and 53.7 mg. and whose beta fractions were 5 per cent and 8 per cent. Two other patients had adrenal cortical tumors. One had a high level of 17-ketosteroid excretion (192.8 mg.) and the other showed a moderate increase (71 mg.). The beta fraction, however, was high in both cases—38 and 27 per cent. Wilkins<sup>63</sup> reported two interesting cases. One was a boy, aged 5, with gynecomastia in whom an adrenal tumor was successfully removed. His level of excretion was only slightly increased (4.1 mg.). The other patient was a girl of the same age with virilism due to an adrenal carcinoma. Her level of excretion was 22 mg. before operation. Afterwards it dropped to 0.9 mg. but 11 months later had risen to 126 mg. She was re-operated upon and the level dropped to 16 mg., but three and one-half months later was back up to 124 mg. The beta fraction in this patient was less than 1 per cent.

FSH determinations in this group numbered 14 and 13 patients.

Those in the two cases of marked adrenal cortical hyperplasia briefly mentioned above were as follows:

*Female*, age 12 (17 KS—75.6 mg.)—positive at 9.5 mouse units and doubtfully positive at 19 mouse units per 24 hours.

*Female*, age 16 (17 KS—95.5 mg.)—positive at 9.1 mouse units and doubtfully positive at 18.2 mouse units. Negative at 46 mouse units per 24 hours.

Of the remaining 11, 10 showed precocious puberty and one, a female, aged four, was a pseudohermaphrodite. All were under nine years of age. The values in seven were negative for the lowest level test, which varied from 2.8 to 6.6 mouse units per 24 hours. The remaining four showed levels as follows:

*Female*, age 7—positive, 11.5 m.u.—negative, 23 m.u.

Same patient, age 8—positive, 8.0 m.u.—negative, 12 m.u.

*Female*, age 8—positive, 3.2 m.u.—negative, 19.2 m.u.

*Female*, age 5—positive, 3.2 m.u.—negative, 19.2 m.u.

*Female*, age 8—positive, 4.8 m.u. per 24 hours—highest level tested.

Apparently, a slight increase in FSH is seen in about half of these cases.

Nathanson and Aub<sup>77</sup> in 1943 reported a high level in a boy of four and one-half years with precocious puberty (positive at 120 mouse units). Wilkins<sup>83</sup> in 1948 reported a level of under 6.5 mouse units in the boy with gynecomastia and an adrenal tumor mentioned above.

### HIRSUTISM

This finding in females has been the reason for many of our tests for 17-ketosteroids. One hundred and thirteen determinations were made in 98 patients. Some of the patients had amenorrhea, some were obese, and one was pregnant, but otherwise there were no apparent endocrine complications. All patients were females and two were young, aged five and six. They both excreted 1.6 mg. per 24 hours—within the normal range for that age.

In the 96 adult females the excretion ranged from 2.3 mg. to 44.2 mg. with an average of 15.2 mg. total neutral per 24 hours. This is somewhat above the normal average of 9.6 mg. and even slightly above our normal range (6 to 12.5 mg.) but the difference is not enough to be of any diagnostic significance. In the patient who was pregnant, the values were 16.1 mg. and 18.1 mg. during the pregnancy and 11.8 mg. after delivery.

The values in some of the patients tended to drop after therapy with estrogens, i.e., from 24.3 mg. to 15.9 mg.—from 12.6 mg. to 10.8 mg.—and from 13.6 mg. to 10.2 mg. However, these figures are not conclusive as they are within the limits of the normal diurnal variations.

Baumann and Metzger<sup>60</sup> in 1940 reported on two patients with simple hirsutism. Both showed slightly high levels but the beta fractions were not elevated. Fraser et al.<sup>43</sup> in 1941 reported on one patient who showed a high normal level of excretion of 17-ketosteroids. Raices et al.<sup>80</sup> in 1945 reported on 75 patients. They found the values to be normal in 26 and high in 49. Of the latter group, 22 were 30 mg. or over. It is of interest that their paper is from Buenos Aires where a higher percentage of the women might be expected to be slightly hirsute. Salter et al.<sup>61</sup> in 1946 reported on eight patients. Four were normal and the rest slightly elevated. In 1947 Venning

and Browne<sup>28</sup> reported four patients with moderate elevations and Talbot et al.<sup>30</sup> reported three patients in whom the excretion levels were normal in one and slightly elevated in the other two.

Studies of *FSH* were made 14 times in 13 patients of this group. Two showed negative tests at 9.1 and 11.3 mouse units, the lowest tested, and eight were definitely within normal limits. One patient showed a possible increase, with a positive test at 51 mouse units and a negative one at 96 mouse units per 24 hours. Two, both of whom had amenorrhea, showed definitely increased levels as follows:

Female, age 24—positive at 96 mouse units  
negative at 192 mouse units

Female, age 19—

(1)—positive at 96 mouse units  
negative at 192 mouse units

age 20—positive at 125 mouse units  
doubtfully positive at 194 mouse units

The majority of the patients therefore were within the normal range. It seems possible that the two patients with the high values might belong in a different category.

#### ADDISON'S DISEASE

*17-Ketosteroids* were measured 16 times in 12 patients. All were adults and seven were males. In the males, the variation was from 1.0 mg. to 9.7 mg. with an average level of 4.2 mg. total neutral per 24 hours. A value of 1.1 mg. was found in a patient aged 31 who was also a eunuch, having had both testes and one kidney removed because of tuberculosis. Another level in this same man was 3.7 mg. Both were taken while he was under treatment with desoxycorticosterone acetate and methyl testosterone linguets.

Excretion in the five female patients varied from 1.5 mg. to 11.2 mg. with an average of 5.6 total neutral per 24 hours.

The high level was in a patient aged 30 who was taking desoxycorticosterone acetate. This drug is not supposed to cause significant change in the level of excretion.

Low levels would be expected in this disease, especially in the female patients. However, in our group, the average in the male patients was the lowest, while that in the woman patients was only slightly below normal range. This difference from expected levels is also found occasionally in the literature as will be noted in the following short survey.

In 1940 Callow et al.<sup>84</sup> reported low levels in seven cases. The next year Fraser et al.<sup>43</sup> reported five female patients with values under 0.5 mg. and three male patients in whom the average levels of excretion were 2.1, 2.6 and 3.5 mg. In 1942 Cuyler et al.<sup>51</sup> reported low levels in two cases and noted that the values were further depressed by treatment with desoxycorticosterone or adrenal cortical extract. Luft<sup>78</sup> in 1943

reported five female patients. The excretion in one was reported as 0, in another it was 2.5 mg., but the remaining three were within normal limits (6.4, 9.8 and 14.8). In two of these patients the values dropped after the administration of desoxycorticosterone. Hoffman<sup>70</sup> in 1944 reported five females with values of less than 0.5 mg. and three male patients with excretion values of 1.2 to 6.4 mg. Salter et al.<sup>91</sup> in 1946 reported six female patients. One was a child of five and one-half years who showed a level of 0.4 mg. In the five adult females, values were from 1.4 to 8.6 mg. One male patient, aged 22, excreted 8 to 10 mg. per 24 hours, with some increase following desoxycorticosterone acetate. In 1947 Venning and Browne<sup>28</sup> reported three female patients with low levels of 2.5, 4.5 and 1.9 mg. and one male with an excretion of 2.8 mg. Talbot et al.<sup>30</sup> reported three females with excretion levels of 0.8, 1.0 and 2.6 mg. and 11 males in whom the values ranged from 1.9 mg. to 4.4 mg. McCullagh et al.<sup>85</sup> in 1948 reported low levels in 13 males and very low levels in seven females. It has been suggested by some that the higher levels reported above may be due to contaminating chromogens that are not true 17-ketosteroids.

FSH levels were measured in two patients and were within normal limits. The values were as follows:

Female, age 45—positive 5.8 m.u./24 hours  
negative 46.2 m.u./24 hours  
Female, age 30—positive 3 m.u./24 hours  
negative 60 m.u./24 hours

McCullagh et al.<sup>85</sup> in 1948 reported normal levels of FSH excretion in seven male patients but in seven female patients, two were normal while the remaining five were high. All of the latter had associated menopausal symptoms.

### EUNUCHOIDISM

Twenty-two estimations of 17-ketosteroid excretion were made in 15 patients. Only one female patient was in this group, a girl of 15, who showed a level of excretion of 7.6 mg. per 24 hours. This is within normal limits, and slightly above average for her age.

The 15 male patients were from 15 to 35 years of age and their range was from 0.3 to 25.2 mg. with an average of 9.0 mg. total neutral per 24 hours. This is somewhat low, being slightly under the normal range. The lowest level was in a patient of Dr. Kinsell. He has reported him<sup>86</sup> as a "panhypopituitary eunuchoid." FSH levels were also low in this patient.

Reaction to treatment with pregnant mare's serum was measured in one patient. His levels before starting were 13.8 mg. and 9.3 mg. per 24 hours, and after one month of treatment the level was 20.6 mg. per 24 hours.

In 1940 Callow et al.<sup>84</sup> reported on five male eunuchoids. All were normal with three in the lower part of the normal range and two in the higher. Fraser et al.<sup>43</sup> in 1941 reported on 11 males and two females. The males were slightly low in nine instances varying from 2.8 to 6.4 mg. and low normal in two others (8.4 and 8.5 mg.). The two females were near the lower limits of normal (5 and 6 mg.). Hoffman<sup>70</sup> in 1944 reported low, low normal, and normal values in eunuchoidism. Heller and Nelson<sup>87</sup> in 1945 reported five eunuchoid males with values ranging from 0.6 mg. to 6.9 mg. Ten moderately severe eunuchoids had moderately low values. Salter et al.<sup>91</sup>



in 1946 reported three males with values ranging from 7.2 to 17 mg. In one patient the beta fraction was as high as 21 per cent. Wall and Hurxthal<sup>85</sup> reported a male, aged 39, in whom excretion levels of 45 and 25 mg. were found. They believed that this patient's adrenals were over-functioning. McCullagh et al.<sup>85</sup> in 1948 reported values of about half the normal average in six male eunuchoids.

*FSH* was measured 19 times in 13 patients. Two females were in this group and both were high, as follows:

Female, age 20—positive 192 m.u./24 hours  
                                   doubtful positive 288 m.u./24 hours  
                                   negative 384 m.u./24 hours  
 Female, age 41—positive 288 m.u.  
                                   positive 524 m.u.  
                                   positive 376—negative 565 m.u./24 hours

Of the 11 male patients, two were quite low. The patient of Dr. Kinsell referred to earlier, showed negative tests at levels of 3.5, 4.2 and 4.2 m.u./24 hours.

Another man of 34 with a typical eunuchoid picture showed an excretion level under 6.2 m.u. per 24 hours (negative at that level). Further study revealed that he had a chromophobe pituitary adenoma. These two cases might be better classified as primarily hypopituitary in view of their urine hormone studies, although the clinical picture was more typical of eunuchoidism. Six of the male patients were definitely within normal limits and two others were at least normal with positive tests at 3.6 m.u. and 32.4 m.u. per 24 hours, the highest levels tested. Two patients were definitely high (positive at 200 m.u. and 92 m.u. per 24 hours) and one patient was probably high (positive at 61 m.u. and doubtful positive at 108 m.u.). These last three probably should be classified as hypergonadotropic eunuchoidism, and may belong to the group that has been described by Heller and Nelson.<sup>87</sup>

McCullagh et al.<sup>85</sup> in 1948 reported high values (105 to 318 m.u. per 24 hours) in six male patients.

### HYPOGONADISM

A number of cases with this diagnosis were tested for *17-ketosteroids*. Fourteen patients were in the group and 15 tests were run. Two female patients showed values of 20.3 mg. and 11.8 mg. per 24 hours. Two female castrates were also examined. The first, a girl of eighteen and one-half, showed a level of 6.2 mg. per 24 hours, and in the second, a woman of 30, the value was 3.4 mg. Twelve male patients showed levels of excretion varying from 2.9 mg. to 20 mg. with an average of 10 mg. total neutral per 24 hours. This average was lower than the normal average but within the normal range. It was not quite as low as the average level in the eunuchoids. The highest figure was in a patient who had developed typical hypogonadism following a severe genito-urinary infection.

Callow et al.<sup>84</sup> in 1940 reported normal levels in a female castrate of 16. Fraser et al.<sup>48</sup> in 1941 reported on four female castrates and found all to be within the normal range. They also reported on three male eunuchs in whom the levels were slightly low (3.2 to 4.1 and 7.0 mg.). Eleven male eunuchs were also reported by Callow et al.<sup>84</sup> who found the 17-ketosteroids in all to be normal but below the average. Hoffman<sup>70</sup> in 1944 reported that the excretion in male eunuchs was within the range of normal females. McCullagh et al.<sup>85</sup> in 1948 reported that five male castrates showed levels of about one-half the normal average.

Low normal levels in hypogonadism were reported in three patients by Luft<sup>78</sup> in 1943. Salter et al.<sup>61</sup> in 1946 reported a normal level in a hypogonad boy of 13. In this patient the beta fraction was 14 per cent. Venning and Browne<sup>28</sup> in 1947 reported slightly low levels (6.7 and 4.1 mg.) in one hypogonad male aged 40.

*FSH* was determined 23 times in as many adult patients with this diagnosis. Five were males with four being within normal limits. The fifth was high with a positive test at 96 mouse units and a negative at 192 mouse units per 24 hours. The patient was a man of 38 who had developed hypogonadism following a testicular infection.

Of the 18 female patients, eight were definitely within normal limits, and seven others were probably normal. Three patients showed definitely high values as follows:

- |                  |                                 |
|------------------|---------------------------------|
| Female, age 35   | —positive at 96 m.u.            |
|                  | doubtfully positive at 192 m.u. |
|                  | negative at 288 m.u./24 hours   |
| Female, age 29   | —positive at 96 m.u.            |
|                  | negative at 192 m.u./24 hours   |
| Female, age 18½— |                                 |
| castrate         | positive at 288 m.u./24 hours   |
|                  | negative at 384 m.u./24 hours   |

Catchpole et al.<sup>89</sup> in 1942 reported on four castrated men. Three showed normal levels of *FSH* and one was slightly high. Hamilton et al.<sup>90</sup> in 1945 reported on four males who had been castrated before puberty—two showed high levels and two normal levels. McCullagh et al.<sup>85</sup> in 1948 reported high levels in four eunuchs. Catchpole et al.<sup>89</sup> also reported two hypogonad men, one with normal and one with slightly high levels of excretion. They noted a fall to normal levels with alleviation of flashes after treatment with testosterone propionate, and did not feel that methyl testosterone was as effective in this regard.

#### HYPOSPADIUS—CRYPTORCHIDISM

*17-Ketosteroids* in a boy aged three with hypospadias were 0.8 mg. per 24 hours. In another boy aged 11, with cryptorchidism, the value was 10.3 mg. total neutral per 24 hours, somewhat above the normal range of 1.5 to 5 mg.

*FSH* was measured in one boy of nine with cryptorchidism, and found to be negative at 4.8 mouse units, apparently within the normal range.

## OVARIAN APLASIA

In this condition, which has been relatively recently described (congenital aplasia of the ovaries, sexual infantilism, short stature, other congenital abnormalities, and high urinary gonadotropins<sup>91</sup>), the *17-ketosteroids* were estimated 10 times in 10 patients.

One patient, aged twelve and one-half, had a level of 1.4 mg., just below the normal range for her age. Another, aged fifteen and one-half, excreted 7.6 mg. per 24 hours—near the normal average for her age. The remaining eight were of adult age and showed values ranging from 1.6 mg. to 23.6 mg. with an average of 8.6 mg. total neutral per 24 hours. Five of the eight values were within normal range and the average figure was only slightly below the normal.

Fraser et al.<sup>43</sup> reported on *17-ketosteroids* in five similar cases. All were of adult age and the average values in all were low, varying from 1.6 to 4.7 mg. per 24 hours.

*FSH level* is most important in the diagnosis of this condition and the values were all high, when the patients were not being treated with estrogens. Twenty-four tests were performed on 14 patients.

Before treatment the values were all elevated, showing positive tests at levels of 27.2 m.u. in the patient aged twelve and one-half, 288 mouse units in a patient aged fifteen and one-half, and in the patients of adult age, 300, 288, 384, 360, 192, 288, 384, 384, 96, 96, 184, 80 and 165 mouse units per 24 hours.

Reactions to treatment with estrogens were of considerable interest. One patient, a woman of 32, had been positive at 300 mouse units, but after one year of treatment with stilbestrol, the urine was positive at 9.2 mouse units and negative at 28 mouse units—within the normal range. After one month without treatment, the level had risen again to positive at 192 mouse units and negative at 288 mouse units. Another patient who was positive at 288 mouse units before treatment dropped to negative at 4.7 mouse units after estrogenic therapy.

Thus, in diagnosing this condition it is important to have the patients off of estrogens for a time (probably one month) before testing for *FSH* level. The high level which is so important in diagnosis will not be present if they are on estrogenic therapy.

## CONGENITAL APLASIA OF THE UTERUS

One patient with this condition, a girl of 16, was studied. Her *17-ketosteroids* were 6.1 mg. per 24 hours—within normal limits, and her *FSH* excretion was under 10.8 mouse units per 24 hours, probably within normal limits.

## GYNECOMASTIA

*17-Ketosteroids* were run in six male patients with this condition. Two boys of 15 showed values of 14.3 mg. and 9.7 mg. per 24 hours. The re-

maining four patients were adults and varied from 6.8 mg. to 17.6 mg., with an average of 12.3 mg. total neutral per 24 hours. This is close to the normal average.

Fraser et al.<sup>43</sup> in 1941 reported on three patients with gynecomastia. All were slightly low. Nathanson<sup>92</sup> in 1942 reported on 21 males, aged 12 to 16, with some breast enlargement. Most were in the low range of normal.

*FSH* was also measured in six patients. It was within the normal range in five and possibly high in one, a man of 37, where tests were positive at a level of 60 m.u. and doubtfully positive at a level of 120 m.u. per 24 hours.

Nathanson<sup>92</sup> in 1942 reported on 16 boys, aged 12 to 16, with some breast enlargement. In the excretion of *FSH*, 13 were normal. In one it was slightly elevated, and in two it was high.

### PREGNANCY

*17-Ketosteroids* were measured five times in four patients during pregnancy. The value varied from 10 mg. to 19 mg. with an average of 15.8 mg. total neutral per 24 hours. This is slightly higher than the normal range.

Fraser et al.<sup>43</sup> in 1941 reported on three pregnant women—one was high normal and two were low normal. Values tended to be lower after delivery. Benda and Bixby<sup>74</sup> in 1947 reported high normal levels in two women. Dobriner et al.<sup>67</sup> reported normal levels in one patient.

### AMENORRHEA

In this group were placed cases with this symptom who did not show enough clinically to be classified under another endocrine diagnosis. Eighteen patients were investigated for *17-ketosteroid* excretion and values varied from 3.6 mg. to 21.2 mg., with an average of 9.9 mg. total neutral per 24 hours. Although this range is somewhat wider than normal, the average is almost exactly normal.

Fraser et al.<sup>43</sup> in 1941 reported on seven such patients. Three showed normal levels, three were slightly low, and one was slightly high. Klinefelter et al.<sup>4</sup> in 1943 reported nine patients. Of these, five showed normal levels and four were slightly low. Salter et al.<sup>61</sup> in 1946 reported low normal levels in a patient with amenorrhea and persistent lactation.

*FSH* was measured in 10 patients of this group. It was normal in four, and probably normal in two more who showed values of (1) positive at 30 m.u., negative at 100 m.u., and (2) positive at 15 m.u./24 hours, highest level tested. Two other patients were negative at the lowest levels tested—12.8 m.u. and 9.6 m.u.—and the two remaining patients were high with levels as follows:

- (1) female age 21—positive 192 m.u., negative 288 m.u.
- (2) female age 21—positive 149 m.u., negative 298 m.u./24 hours.

Klinefelter et al.<sup>4</sup> in 1943 reported on 10 women. Three were low and seven were within normal limits, including three patients whose amenorrhea had developed post partum.

### MENORRHAGIA—DYSMENORRHEA

*17-Ketosteroids* were measured in two patients aged 19 and 16 with menorrhagia. One value was normal at 8.2 mg. and the other was slightly low at 4.9 mg. total neutral per 24 hours.

*FSH* was tested in one girl aged 16 with dysmenorrhea and was found to be normal.

### CLIMACTERIC

*17-Ketosteroids* were tested 16 times in 15 patients with suggestive symptoms.

Three were females aged 32, 60 and 63 years, and the values were 11 mg., 5.2 mg., and 7.9 mg. total neutral per 24 hours respectively.

Twelve males showed levels ranging from 6.4 mg. to 31.7 mg., with an average of 13.6 mg. total neutral per 24 hours. This is only slightly below the normal average. Two of the men were elderly, aged 70 and 76, and their excretion levels were both below the normal range (6.7 and 7.4 mg. in the first patient and 6.4 mg. in the second).

Fraser et al.<sup>43</sup> in 1941 reported on three women aged 45, 63 and 60. The first two showed low normal values (6 and 7 mg.) and the third was slightly low (3.8 mg.). Salter et al.<sup>61</sup> in 1946 reported low values (1.6 mg.) in a senile man of 78. Hoffman<sup>70</sup> noted that 17-ketosteroid values were low in extreme old age.

*FSH* excretion was tested in 24 patients. Twelve were females. Of these, four showed the high levels that are considered typical of this condition (positive at 192 m.u., 132 m.u., 120 m.u. and 120 m.u. per 24 hours). The ages of these patients with the high levels were 48, 52, 44 and 65 years. Four patients aged 43, 33, 43 and 45 years were normal and three more aged 32, 40 and 43 were probably normal with values of (1) positive at 24.6 m.u., doubtful positive at 50 m.u., negative at 96 m.u., (2) positive at 24.8 m.u., doubtful positive at 74.4 m.u., negative at 96 m.u., (3) negative at 50 m.u. One patient aged 33 was negative at 6.2 m.u. per 24 hours. She also had hyperthyroidism with diabetes.

Thus the higher levels in this series occurred only in older women, with younger women having normal levels, even though they showed suggestive symptoms. The absence of high *FSH* excretion may cast some doubt upon the diagnosis of menopause in the latter group.

Of the 12 male patients, three were high, with positive levels at 80, 96 and 170 m.u./24 hours. Their respective ages were 46, 38 and 46 years. Five were normal (aged 76, 46, 47, 55 and 49 years), and three were probably normal (aged 53, 51 and 50). Their levels were:

- (1) doubtful positive at 12.1 m.u., negative at 24.2 m.u.
- (2) doubtful positive at 9 m.u., negative at 20 m.u.
- (3) negative at 24 m.u./24 hours.

One patient was difficult to interpret, having only a single test at a level of 192 m.u. which was negative.

Thus the high levels were not as frequent in the male patients, and it is probable that the diagnosis of the male climacteric will not be made more certain with any greater frequency by the use of this test.

#### GONADAL TUMORS

*17-Ketosteroids* were tested in two patients aged 42 and 62 with testicular tumors. The values were 9.6 mg. and 8.5 mg. total neutral per 24 hours, both slightly below the normal range.

*FSH* was tested in one boy aged 16 with possible recurrence of a chorionepithelioma that had been removed four months before. The excretion was high, with a positive test at 120 m.u. and a negative one at 300 mouse units.

*17-Ketosteroids* were measured in a female aged 40 with a granulosa cell tumor of the ovary. The level of excretion was slightly low at 4.6 mg. per 24 hours.

Salter et al.<sup>61</sup> reported slightly elevated levels in a girl of three and one-half with a granulosa cell tumor of the ovary.

#### POLYCYSTIC OVARIES

##### (HYPERTHECOSIS)

*17-Ketosteroids* were tested 11 times in five patients with this condition.

One woman aged 21 with menorrhagia had a normal level of excretion at 10.8 mg. per 24 hours. Two other patients with considerable hirsutism had normal values of 7.7 and 6 mg. per 24 hours. The two remaining patients were also hirsute and had high levels of excretion—both were tested again after operation as follows:

Female aged 18—23.2 mg. per 24 hours before operation and 18.5 and 20.3 mg. after operation.

Female aged 21—26.5 mg., 16.8 mg. and 22.1 mg. per 24 hours before operation and 16.8 and 21 mg. total neutral per 24 hours after the operation. Thus the values dropped slightly but not significantly.

*FSH* was tested five times in four of the patients. It was normal in three and elevated (positive at 96 m.u. and negative at 192 m.u.) in the one patient who had menorrhagia.

#### PHEOCHROMOCYTOMA

*17-Ketosteroids* were tested in a man of 46 with this condition. The level was slightly low, at 7.9 mg. total neutral per 24 hours.

## OLIGOSPERMIA, STERILITY, LOSS OF POTENCY

*17-Ketosteroids* were tested in three men with the above diagnoses. Results were as follows:

- (1) Age 34—10.2 mg. per 24 hours
- (2) Age 32—17.2 mg. per 24 hours
- (3) Age ? —23.8 mg. per 24 hours

Therefore all were normal or only slightly above normal.

Fraser et al.<sup>43</sup> reported normal levels in two patients with functional impotence—McCullagh<sup>85</sup> reported that six patients with oligospermia showed normal levels of excretion.

*FSH* was estimated in one patient with oligospermia and in two male patients who were sterile. It was normal in two and possibly increased in one of the latter (values positive at 51 m.u. and negative at 96 m.u. per 24 hours).

McCullagh et al.<sup>85</sup> reported that his six patients with oligospermia showed high *FSH* levels (105 to 480 m.u.).

## OBESITY

*17-Ketosteroids* were measured in eight cases. Three between the ages of 10 and 15 showed excretion of 3.7 mg., 8.4 mg., and 8.7 mg. total neutral per 24 hours—all within normal limits. Of the five adults, four were females and showed the following levels of excretion—11.9 mg., 11 mg., 5.6 mg. and 14.1 mg. total neutral per 24 hours. The one man aged 40, who was very obese, showed moderate hypogonadism and had hyperostosis frontalis interna. His level was normal at 14.1 mg. per 24 hours. Thus all were within or near the normal range.

Talbot et al.<sup>69</sup> in 1943 reported on nine obese children in whom the average of *17-ketosteroid* excretion was normal. Another group of seven very obese children showed slight elevation of the *17-ketosteroids*. Nathanson and Aub<sup>77</sup> reported on nine children aged 10 to 16 with adiposogenital dystrophy. In all, the *17-ketosteroids* showed excretion that was normal or slightly elevated. Salter et al.<sup>61</sup> in 1946 reported that a male patient of 26 with obesity and gigantism showed a slightly low level of *ketosteroid* excretion.

*FSH* was run in two instances, but with negative results. The man aged 40 just mentioned above had a single negative result at a level of 30 m.u. and a very obese girl of 15 had a single negative test at a level of 100 m.u. per 24 hours.

Nathanson and Aub<sup>77</sup> reported normal *FSH* excretion in eight patients aged 10 to 16 with adiposogenital dystrophy.

## ALOPECIA

Six patients with this condition in varying degrees were tested for level of *17-ketosteroid* output. One girl of fourteen and one-half excreted 6.2

mg. per 24 hours—a normal amount. Three adult females showed values of 20.8 mg., 17.3 mg., and 4.8 mg. total neutral per 24 hours, the figures being both slightly higher and slightly lower than the normal range. Two male patients also showed high normal and slightly low values—17.8 mg. and 6.8 mg. per 24 hours.

Salter et al.<sup>61</sup> reported normal values in a male of 18 with alopecia.

*FSH* was measured in four of these cases and all were within the normal range.

### FEVER, ASTHMA, ARTHRITIS

*17-Ketosteroids* in three patients with fever, all adult females, were slightly low in two. The values were 3.8 mg., 4.5 mg., and 8.0 mg. One patient with asthma, a male aged 30, was low, with a level of 4 mg. per 24 hours, and one female patient with arthritis aged 29 was within the lower ranges of normal with a level of 6.5 mg./24 hours.

Fraser et al.<sup>43</sup> reported low levels in two patients with arthritis. Davison, Koets and Kuzell<sup>93</sup> studied 13 male patients with Marie-Strumpel type of arthritis and found moderate elevation of 17-ketosteroid output with levels varying from 19.2 mg. to 43.7 mg. with an average of 27.3 mg. Eleven females with rheumatoid arthritis varied from 3.5 to 21.6 mg. with an average of 12.8 mg. This is slightly above the normal average, but within the normal range. Forbes et al.<sup>45</sup> in 1947 studied the output in chronic disease and found it to be generally moderately decreased. A group of 82 male patients with an average age of 44 showed an average output of 6.2 mg., and 114 females of an average age of 37 showed an average output of 4.4 mg.

### MISCELLANEOUS

*17-Ketosteroids* were tested in individual cases of the following conditions:

*Osteoporosis.* Female aged 56—15.3 mg. per 24 hours.

*Congenital Lipodystrophy.* Female aged 26—23.9 mg. per 24 hours.

*Myotonia Atrophica.* Male aged 42—9.0 mg. per 24 hours.

*Epilepsy.* Male aged 34—14.6 mg. per 24 hours. After one shock treatment the value was 16.6 mg. and after 10 shock treatments the level was 21.3 mg. per 24 hours.

Fraser et al.<sup>43</sup> reported two women with osteoporosis. One aged 63 had a low normal level of 6 mg., and the other aged 60 showed a slightly low level of 3.8 mg. They also reported on two women with myasthenia gravis. One was normal at 8.5 mg. and the other slightly low at 4.3 mg. Benda and Bixby<sup>74</sup> in 1947 reported five males and one female with myotonia dystrophica. All were moderately low, the male patients excreting from 4.8 to 8 mg., and the one female showing a level of 2.8 mg. per 24 hours.

*FSH* was tested in one case of von Gierke's disease in a male aged 18 and showed normal levels.



The following results are from some studies made at the Langley Porter Clinic under Dr. Karl M. Bowman, Dr. A. Simon and Dr. N. Halliday and are included with their permission. They represent a small sampling of an extensive problem, the results of which are now in press in the *Journal of Nervous and Mental Disease*.

### HOMOSEXUALS

*17-Ketosteroids* were tested in five patients and all were normal, though in the higher ranges. Three male adults showed values of 12.3 mg., 18 mg. and 17.9 mg. Two females excreted 13.7 mg. and 14.2 mg. total per 24 hours.

Benda and Bixby<sup>74</sup> reported on eight male and two female homosexual patients. The 17-ketosteroids in the males were normal in five and slightly low in three. The two females showed normal ranges of excretion.

*FSH* was tested in two of these patients, both of whom were transvestites. The male patient (dressed as a female) showed normal levels, but the female aged 25 had a high excretion with a positive test at a level of 192 mouse units per 24 hours.

### MANIC DEPRESSIVE PSYCHOSIS

*17-Ketosteroids* were measured six times in two patients. The one male patient showed levels of 13.4 mg., 16.6 mg. and 16.2 mg. total neutral per 24 hours and the female excreted 11.7 mg., 9.9 mg. and 13.2 mg. per 24 hours. These were all within or close to the normal range.

### INVOLUTIONAL DEPRESSION

*17-Ketosteroids* were measured three times in two male patients. The values were 14.2 mg., 24.1 mg. and 21 mg. per 24 hours.

### SCHIZOPHRENIA

Twenty-three measurements of *17-ketosteroids* were made in 11 patients. Nine were males, and showed levels varying from 5.2 mg. to 20.5 mg. with an average of 12.9 mg. total neutral per 24 hours. Two female patients were in the group—one aged 26 excreted 15.4 mg. per 24 hours on two occasions. The other aged 17 had amenorrhea and showed levels of 10.2 mg., 10.7 mg., 15.9 mg. and 14.7 mg. per 24 hours. After therapy, this patient showed levels of 11.5 and 14.8 mg. Thus values were normal in the males, and tended to be slightly high in the females.

### ANXIETY NEUROSIS

*17-Ketosteroids* were tested eight times in five patients with this diagnosis. In two males the values were normal, being 12.8 and 12.6 mg.

In three females, the range was from 10.1 mg. to 18.6 mg. per 24 hours, with an average of 15.9 mg.

Thus again the males were within normal limits, and the females tended to be slightly high.

### SUMMARY AND CONCLUSIONS

The availability of a chemical test for measuring 17-ketosteroids in the urine has stimulated more general interest and research in this field of urinary hormonal assays. A review of tests now being used reveals that most are biological assays requiring the use of animals. Outlines of the methods used in most of the tests are given.

Tests more generally available at this time are: those for detecting pregnancy and those for measurement of 17-ketosteroids, follicle-stimulating pituitary gonadotropin, and pregnandiol. Tests for measuring estrogens and the glycogenic adrenal corticoids give promise of more widespread clinical acceptance.

Experience with 488 tests for 17-ketosteroids and 233 tests for FSH at the University of California Hospital has been reviewed. Normal ranges from our experience were compared with those of other authors.

Low values for 17-ketosteroids were found in the following conditions: Hypophyseal infantilism, Simmonds' disease, anorexia nervosa, Addison's disease, myxedema and severe asthma. The average for Simmonds' disease was lower than that for anorexia nervosa, but there was overlapping in the ranges of the two.

High levels of 17-ketosteroid excretion were found in adrenal cortical carcinoma and hyperplasia. When further separation into alpha and beta fractions of the 17-ketosteroids was done, the beta fraction was particularly elevated in the patients with carcinoma. However, one patient with adrenal cortical carcinoma showed normal values.

Slightly high levels of 17-ketosteroids were found in patients with simple hirsutism, Cushing's syndrome, acromegaly, pregnancy and hyperthecosis.

Slightly low levels of 17-ketosteroids were noted in eunuchoidism, male and female castrates, diabetes mellitus, occasionally in the male or female climacteric, and in chronic debilitating diseases. There was a tendency toward lower levels in old age.

The slightly high and slightly low levels are of limited clinical value because of the considerable daily variation in 17-ketosteroid output in the same individual, which may cause the level to vary in and out of the normal range.

A long list of conditions showed normal 17-ketosteroid excretion. These included hypogonadism, ovarian aplasia, gynecomastia, simple amenorrhea, oligospermia, obesity, alopecia and various psychiatric disorders.

FSH excretion was measured by bioassay and a definite end-point was more difficult to find. Occasionally it was necessary to test several specimens at various levels.

The excretion level of FSH was always high in ovarian aplasia when the patient was not receiving estrogenic therapy. This is one of the cardinal points in the clinical diagnosis of the condition. It was occasionally high in the male and female climacteric, seeming more consistent in the latter, in eunuchoidism, and in hyperthecosis. A high value was found in one female castrate.

A low level of FSH excretion was noted in patients with hypophyseal infantilism, Simmonds' disease and anorexia nervosa. The latter condition also shows normal levels, but unfortunately again, there was overlapping in the ranges with Simmonds' disease. Some eunuchoids also showed a low level of FSH excretion, and may represent a separate group from those with high values.

Normal values for FSH excretion were encountered in acromegaly, anorexia nervosa, hyperthyroidism, hypothyroidism, Cushing's syndrome, adrenal cortical hyperplasia, simple hirsutism, Addison's disease, gynecomastia, the climacteric, hyperthecosis, oligospermia, and alopecia.

The greatest clinical value of the test for 17-ketosteroids at present is in the high levels found in adrenal cortical hyperplasia and carcinoma, and the low levels of hypophyseal infantilism and Simmonds' disease.

The test for FSH is particularly valuable in its high levels in diagnosing ovarian aplasia and the climacteric. The low levels are of value in pituitary infantilism and Simmonds' disease.

The tests have resulted in a better understanding of some of the clinical syndromes and it is possible that further fractionation of the 17-ketosteroids may considerably increase their diagnostic importance.

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# THE HEMODYNAMIC EFFECTS OF SYMPATHECTOMY IN ESSENTIAL HYPERTENSION\*

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SURGICAL sympathectomy has been employed so extensively for the treatment of essential hypertension that one might assume its hemodynamic effects to be completely understood. Quite to the contrary, however, very little is known concerning its direct vascular or indirect metabolic effects that will explain its success in some cases and its failure in others. Until these matters are fully understood the rationale for surgical treatment, and indeed for medical management, of essential hypertension must remain on an empirical basis. For this reason these problems have been and will continue to be the subject of long-term investigation in this laboratory.

## MATERIALS AND METHODS

Patients with essential hypertension selected for splanchnicectomy<sup>1</sup> have been made freely available for study through the active coöperation of Dr. Reginald H. Smithwick, under whose direction sympathectomy was performed. They were studied before and again, if possible within three weeks after bilateral operation, usually of the lumbodorsal type.<sup>2</sup> In addition, some patients were studied a third time four to 10 months after operation, whereas a few patients were studied only once—from one to nine years post-operatively.

Arterial pressure was measured with a Hamilton manometer<sup>3</sup> attached to a needle in the brachial or femoral artery. Cardiac output was determined by the Fick principle with the intravenous catheter method of Cournand.<sup>4</sup> Hepatic-portal (splanchnic exclusive of renal and adrenal) blood flow was estimated by the bromsulfalein method of Bradley et al.<sup>5</sup> Both before and after operation the patients, while under study, were given a number of vasomotor stimuli designed to produce, if possible, sympathetic nervous vasoconstriction.<sup>6,7</sup> The most useful of these stimuli were (a) tilting the subject into the upright position and (b) having him perform the Valsalva maneuver.

*Cardiac Output.* Confirming the observations of others,<sup>8,9</sup> no great or consistent change was found in basal cardiac output of patients after sympathectomy as compared with before, regardless of how much the arterial

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pressure was lowered (table 1). Thus, the cardiac output and mean\* arterial pressure in three patients studied before *lumbodorsal splanchnicectomy*<sup>2</sup> averaged respectively 5.97 l./min. and 172 mm. Hg, and when repeated in the same patients two weeks after operation they averaged 5.37 l./min. and 142 mm. Hg. Furthermore, when measured a third time 10 months after operation the output in two of these patients again showed no consistent change. Likewise, cardiac output measured after *supradiaphragmatic splanchnicectomy*<sup>12</sup> in two patients, and after *transthoracic extension*<sup>2</sup> of a previous splanchnicectomy in two others, showed no consistent change from the preoperative values (table 1).

TABLE I  
Average Basal Cardiac Output (Direct Fick)  
and Arterial Pressure

Patient	Sex	Age	Surface Area sq. m.	Type of Operation†		Before Sympathectomy		After Sympathectomy			
								2 Weeks		10 Months	
				Previ- ous	Present	Cardiac Output l./min.	Mean* Arterial Pressure mm.Hg	Cardiac Output l./min.	Mean* Arterial Pressure mm.Hg	Cardiac Output l./min.	Mean* Arterial Pressure mm.Hg
Far	F	41	1.55		LDS	7.07	147	5.54	139		
Bus	M	26	1.78		LDS	6.27	179	6.31	125	5.27	130
Pit	F	52	1.55		LDS	4.56	189	4.27	161	5.17	144
Dun	M	30	1.83		SDS	5.79	120	5.89	109		
Bro	M	51	1.79		SDS	3.89	202	4.39	150		
Cra	M	26	1.84	SDS	TTE	5.04	142	6.27	116		
Ret	M	41	2.05	LDS	TTE	7.24	173	6.22	162		
Mean		38	1.77			5.69	165	5.56	137	5.22	137

\* One-half systolic plus diastolic, from direct readings with Hamilton manometer.

† LDS = lumbodorsal splanchnicectomy.

SDS = supradiaphragmatic splanchnicectomy.

TTE = transthoracic extension of previous splanchnicectomy upward to and including the first or second dorsal (thoracic) sympathetic trunk ganglia.

*Hepatic-Portal Blood Flow.* Basal blood flow through the liver as estimated by the hepatic extraction of bromsulfalein was uniformly increased in 10 patients shortly after sympathectomy except in one ("Max") of the seven in whom arterial pressure was already lowered (table 2).<sup>10, 11</sup> Thus, within three weeks following *lumbodorsal splanchnicectomy* hepatic blood flow in eight patients resting in a horizontal position had increased from an average of 1433 to 2018 ml. per minute per 1.73 sq. m. of body surface.† The mean arterial pressure in this group averaged 160 mm. Hg before and 149 mm. Hg shortly after operation. When measured four to seven months later in four

\* Arithmetic mean, calculated simply as one-half the sum of the systolic and diastolic pressures.

† Subsequent values for hepatic-portal blood flow have been corrected likewise to standard body surface area of 1.73 square meters.

TABLE II  
Average Basal Hepatic-Portal Blood Flow and Arterial Pressure in the Horizontal Position

Patient	Sex	Age	Before Sympathectomy		After Sympathectomy					
			HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg	Type of Operation†	Early (10-20 days)		Late (months or years)		
						HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg	Interval	HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg
Dun	M	30	1040	120	SDS	2013	109	Mos.		
Bro	M	51	1134	178	SDS	1363	146			
Max	M	43	1524	132 (s)	LDS	1309	111 (s)	4 6 7 7 10 10		
Pau	M	36	1960	124 (s)	LDS	2360	120 (s)			
She	M	51	1127	138 (s)	LDS	1810	157 (s)		1404	134 (s)
McC	M	43	1558	184 (s)	LDS	2884	184 (s)		1855	178 (s)
Dea	M	54	1334	168 (s)	LDS	2748	152 (s)		1454	184 (s)
Gol	M	31	944	178 (s)	LDS	1327	183 (s)		1168	181 (s)
									1314	167
Bus	M	26	1450	182	LDS	1857	128	10	813	131
Pit	F	53	1563	171	LDS	1851	154	10	1192	156
Oue	F	24	1397	166	TTS			4	1259	105
Yof	F	42			LDS			Yrs. 1 2 3 4 4 9	1169	132
Bar	F	52			LDS				896	153
Ret	M	41			LDS				1356	169
Dem	M	52			LDS				1318	176
Lee	M	35			LDS				866	110 (s)
O'L	F	47			LDS				1347	123

\* One-half systolic plus diastolic pressure.

(s) Taken with mercury sphygmomanometer.

† TTS = total thoracic sympathectomy.

SDS = supradiaphragmatic splanchnicectomy.

LDS = lumbodorsal splanchnicectomy.

of these patients (in whom it had averaged 1241 ml. before, and 2192 ml. shortly after operation), the resting hepatic blood flow averaged 1507 ml./min. In this group the mean arterial pressure averaged 167, 169, and 166 mm. Hg during the first, second, and third tests respectively. In two patients who were not studied the third time until 10 months after operation the resting hepatic blood flow and mean arterial pressure respectively averaged 1507 ml./min. and 177 mm. Hg before, 1854 ml./min. and 141 mm. Hg shortly after, and 1003 ml./min. and 144 mm. Hg 10 months after the operation (figure 1).

In two patients in whom *supradiaphragmatic splanchnicectomy* was done hepatic blood flow and mean arterial pressure respectively averaged 1087 ml./min. and 149 mm. Hg before, and 1688 ml./min. and 128 mm. Hg shortly after operation. In one patient who had a *total thoracic sympathectomy*<sup>2</sup> the hepatic blood flow measured four months (but not earlier) after

operation had declined slightly from the preoperative average of 1397 ml./min. to 1259 ml./min. The mean arterial pressure in this patient had decreased markedly from a preoperative level of 166 mm. Hg to a postoperative value of 105 mm. Hg.

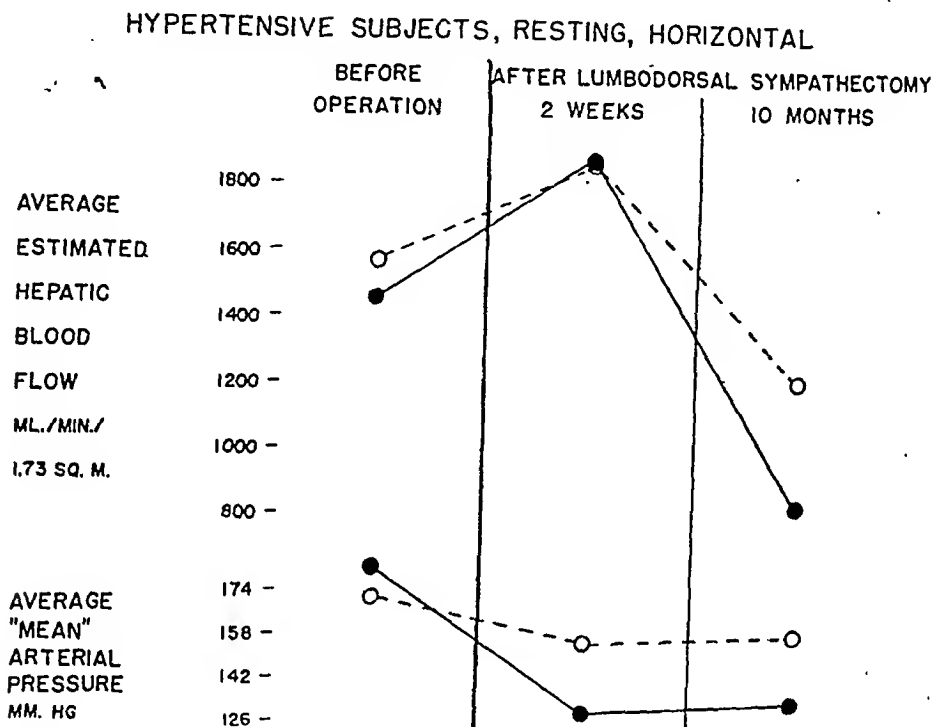


FIG. 1. Chart of average hepatic-portal blood flow and "mean" (one-half the systolic plus diastolic) arterial pressure in two patients—"Pit" (broken lines and circles) and "Bus" (solid lines and dots)—before and after lumbodorsal sympathectomy. Biopsy of the kidneys at operation in "Bus" revealed chronic glomerular nephritis.

Finally, six patients who were studied one to nine years after (but not before) lumbodorsal splanchnicectomy had mean arterial pressures that averaged 144 mm. Hg and hepatic blood flows that averaged 1159 ml./min., a value considerably below the average of 1490 ml./min. for 45 \* normotensive patients<sup>5</sup> and slightly below the average of 1294 ml./min. for 25 unoperated hypertensive patients.<sup>13</sup> Thus, splanchnic vasodilatation apparently was present immediately after operation, whether or not the blood pressure was significantly affected, but over a period of months it slowly moderated.

Tilting the patient into the upright position caused hepatic blood flow in 12 unoperated hypertensive, as in normotensive, subjects consistently to decrease without a proportionate fall in arterial pressure<sup>14</sup> (table 3). This decrease in blood flow in the upright position before operation averaged 31 per cent but was accompanied by only a 2 per cent decrease in average mean arterial pressure. In five of these patients two weeks after the lumbo-

\* Including 23 subjects from the paper cited, 14 additional subjects studied by Dr. Franz J. Ingelfinger, and 8 subjects studied in this laboratory.

TABLE III  
Effects of Upright Posture on Average Basal Hepatic-  
Portal Blood Flow and Arterial Pressure

Patient	Sex	Age	Before Sympathectomy				After Sympathectomy				
			Horizontal		Upright		Inter- val	Horizontal		Upright	
			HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg	HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg		HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg	HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg
Val	M	37	1328	161 (s)	900	157 (s)	Mos.				
Ric	M	33	1205	175 (s)	752	173 (s)					
Cam	M	51	1120	167	1028	173					
Ayd	M	51	1403	162	981	161					
Col	M	28	941	174 (s)	632	160 (s)					
Dun†	M	30	1040	120	652	109	$\frac{1}{2}$	2013	109	878	90
Max	M	43	1524	132 (s)	782	126 (s)	$\frac{1}{2}$	1309	111 (s)	685	75 (s)
Pau	M	36	1960	124 (s)	990	123 (s)	$\frac{1}{3}$	2360	120 (s)	1593	80 (s)
Dea	M	54	1334	168 (s)	993	171 (s)	$\frac{1}{2}$	2748	152 (s)	1913	138 (s)
							$\frac{1}{2}$	1454	184 (s)	1187	169 (s)
She	M	51	1127	138 (s)	817	134 (s)	$\frac{1}{2}$	1810	157 (s)	1500	131 (s)
							$\frac{1}{4}$	1404	134 (s)	982	116 (s)
McC	M	43	1558	184 (s)	1330	185 (s)	$\frac{1}{2}$	2884	184 (s)	1625	133 (s)
							$\frac{1}{6}$	1855	178 (s)	1332	147 (s)
Gol	M	31	944	178 (s)	835	165 (s)	2	1168	181 (s)	927	149 (s)
							7	1314	167	1247	145
Bar	F	52					Yrs. 3 4	896	153	781	124
Lee	M	35						866	110 (s)	770	108 (s)

\* One-half systolic plus diastolic pressure.

† "Dun" had supradiaphragmatic splanchnicectomy.

"Max" and following patients had lumbodorsal splanchnicectomy.

(s) Taken with mercury sphygmomanometer.

dorsal operation, when the hepatic blood flow in the horizontal position (as pointed out above) was greater than before, it tended to decrease in the upright position, but roughly in proportion with the postural fall in arterial pressure, 34 per cent and 23 per cent respectively.<sup>15</sup> Three of these patients studied four to seven months after operation showed a decrease in hepatic blood flow and arterial pressure in the upright position of 26 per cent and 13 per cent, respectively, as compared with the values in the horizontal position. However, collateral evidence indicated that in two, and probably in the third (figure 2), of these patients, splanchnic vasoconstrictor reflexes, though markedly reduced, were not completely abolished. Two patients studied for the first time three and four years after lumbodorsal splanchnicectomy had hepatic blood flows and mean arterial pressures in the horizontal position that averaged respectively 881 ml./min. and 133 mm. Hg. In the upright position these values fell to 776 ml./min. and 116 mm. Hg, decreases of 12 per cent and 13 per cent respectively.

Figure 2 illustrates the effects of splanchnicectomy upon the arterial pressure and the hepatic-portal blood flow of a hypertensive patient ("McC") in both the horizontal and upright positions. Before operation there was a fall in hepatic flow with little change in arterial pressure when the patient was tilted upright. Two weeks after operation, when there was a marked increase in hepatic blood flow and a slightly lower arterial pressure in the horizontal position, only a small decrease in average flow occurred with a striking fall of pressure in the upright position. Six months after operation resting hepatic blood flow had returned toward the pre-operative level and arterial pressure had shown little further change. When the patient was tilted upright, both the arterial pressure and the hepatic blood flow fell, but with a lower pressure the flow was as great as it had been before operation with a high pressure.

These results were interpreted as indicating that early after sympathectomy there was not only a splanchnic vasodilatation in the horizontal position, but also a marked reduction of splanchnic vasoconstriction in response to the upright position. Provided the splanchnic sympathectomy had been rela-

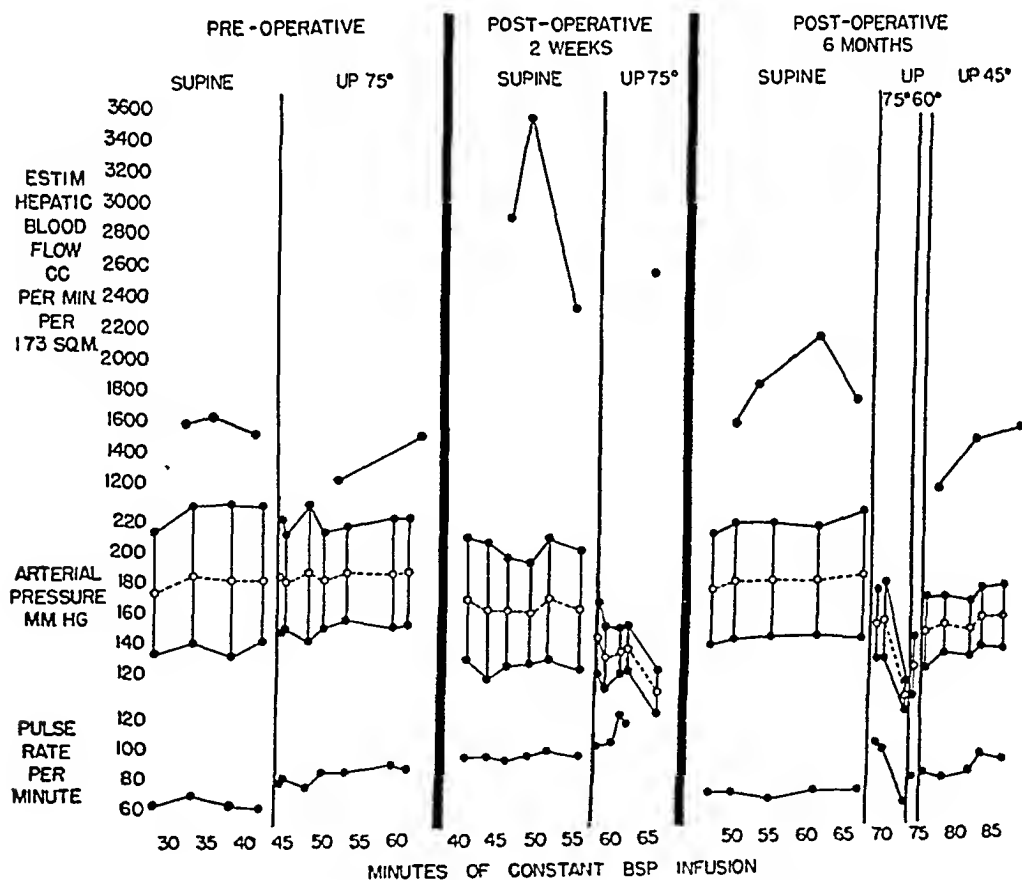


FIG. 2. Chart of estimated hepatic-portal blood flow (EHBF), arterial pressure, and pulse rate of a patient—"McC"—in the horizontal and upright positions, before and after lumbodorsal sympathectomy. During the third test the patient was unable to stand at 75 degrees long enough to allow EHBF to be measured and so was lowered to 45 degrees.

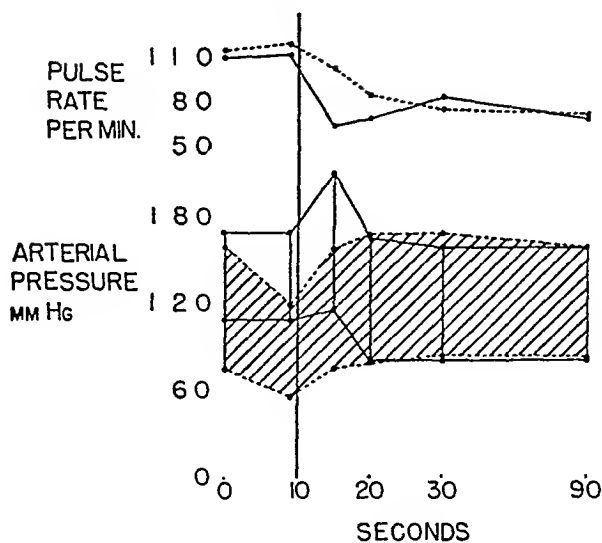


FIG. 3. Chart of the effects of being quickly tilted from the upright (75 degrees) to the horizontal position upon pulse rate and arterial pressure of a patient—"Pau"—before (solid lines and dots) and after (interrupted lines and circles) lumbodorsal sympathectomy.

tively complete, splanchnic vasoconstriction in response to the upright position apparently continued to be slight or absent months to years after the operation, when the early splanchnic vasodilatation had subsided.

*Vasopressor Reflexes.* By recording continuously the arterial pressure before, during and after certain simple vasopressor stimuli it has been possible to detect marked, though brief, reflex vasopressor responses that can be shown to be due largely to splanchnic vasoconstriction.<sup>16, 17, 18</sup> Thus, after the application of blood-pressure-lowering procedures such as a tilt into the

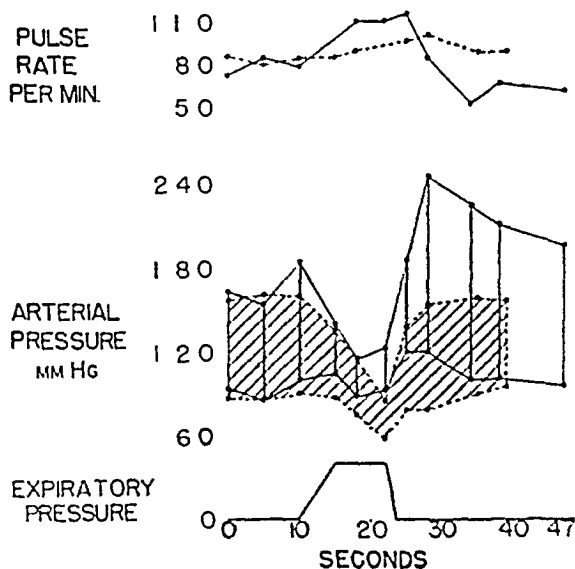


FIG. 4. Chart of the effects of the Valsalva maneuver (10 seconds of forced expiration) in the patient "Pau" before and after lumbodorsal sympathectomy. Other notations as in figure 3.

upright position (figure 3), or the performance of the Valsalva maneuver (figure 4), sharp hypertensive overshoots of arterial pressure were found immediately after stopping the stimuli. For example, upon stopping the Valsalva maneuver (during which venous return to and arterial output from the heart were temporarily diminished and arterial pressure markedly lowered), hypertensive patients, like normal subjects, usually markedly overshoot their basal arterial pressures<sup>6,7</sup> (figures 4, 5, 6).

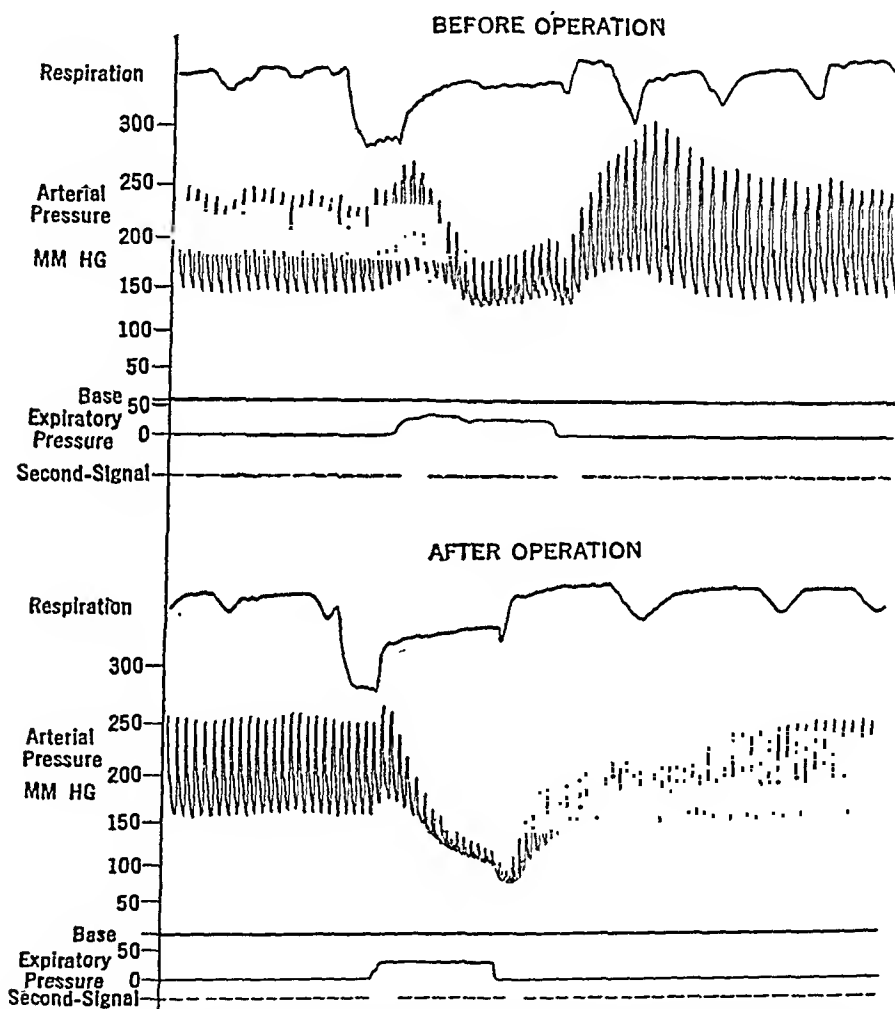


FIG. 5. Optical records of the effects of the Valsalva maneuver on respiration (inspiration down), arterial pressure, and expiratory pressure in a patient, "Rich," before and after lumbar sympathectomy.

Such overshoots of arterial pressure in response to blood-pressure-lowering procedures were completely abolished or greatly reduced shortly after lumbar sympathectomy (figures 3, 4, 5, 6). For example, the overshoot responses when graded in 20 patients (table 4) before this operation were grade IV in 4, grade III in 5, grade II in 9, and grade I in 2; whereas shortly after operation they were negative in all except two patients (grade I). Thus, even those patients who before sympathectomy had overshoot



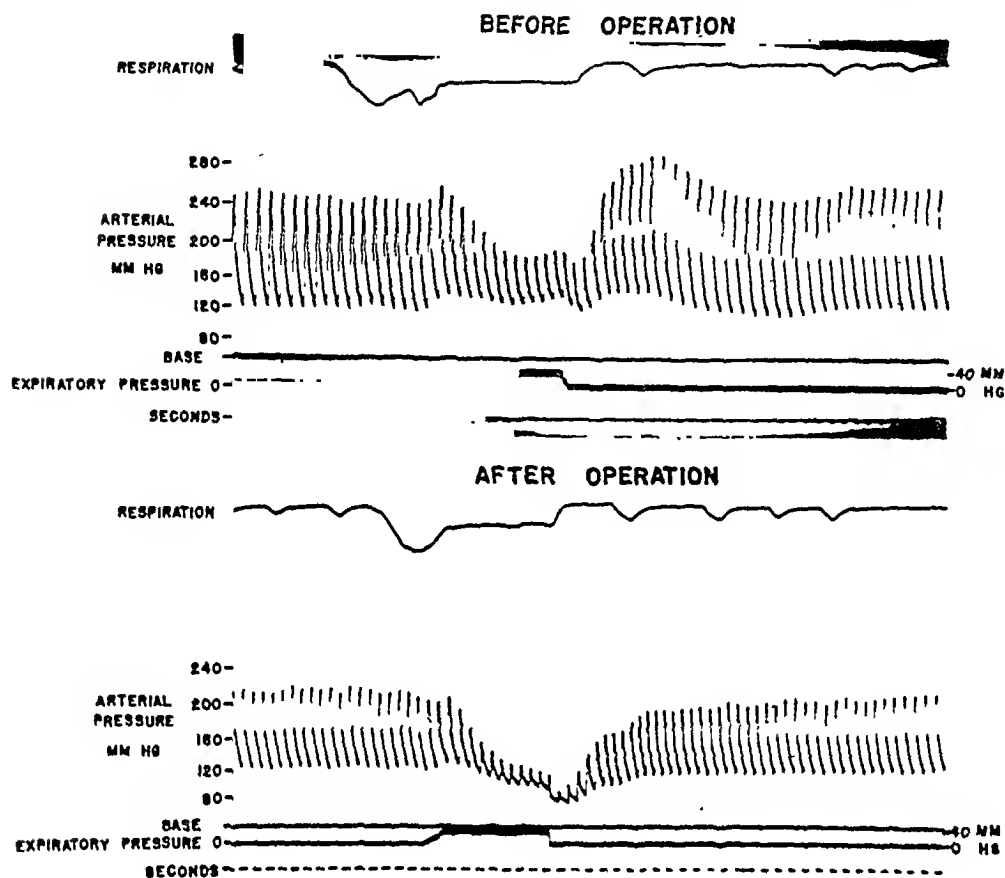


FIG. 6. Optical records of the effects of the Valsalva maneuver in patient "McCl" before and after lumbodorsal sympathectomy. Other notations as in figure 5.

their mean arterial pressures by as much as 35 per cent (grade IV), after sympathectomy had slight or negative (less than 5 per cent) overshoots following these stimuli, restoring their pressures only gradually (during 30 to 60 seconds) from the lowered to the control levels (figures 3, 4, 5, 6).<sup>6,7</sup> Of 12 patients studied five months to nine years after (but not before) lumbodorsal splanchnicectomy, two had grade II, six had grade I, and four had negative responses (table 4).

The reduction or abolition by sympathectomy of such vasopressor overshoots after blood-pressure-lowering procedures seemed to depend upon the type and the amount of the sympathetic nervous tissue removed. Thus, operations less extensive than a lumbodorsal procedure usually failed to abolish the overshoots, while more extensive denervations added little to the effectiveness of the lumbodorsal operation in this regard.<sup>7</sup> Therefore, the amount of these overshoots was helpful in determining the extent and completeness of recent operations on the sympathetic nervous system and also in judging the continued effectiveness of old operations. For example, one patient ("McCl") who had recently undergone an operation elsewhere, presumably a supradiaphragmatic splanchnicectomy, had not been benefited in

TABLE IV  
Overshoot Responses Graded before and/or  
after Lumbodorsal Splanchnicectomy

Patient	Sex	Age	Before Operation		Interval	After Operation	
			Arterial Pressure	Grade		Arterial Pressure	Grade
Tut	M	37	210/117	II	2 weeks	175/108	Neg.
Max	M	43	160/95	II	2 weeks	120/75	Neg.
Pau	M	36	165/95	IV	2 weeks	155/85	Neg.
Far	F	41	200/95	III	2 weeks	170/90	Neg.
Rich	F	29	245/140	III	2 weeks	250/160	Neg.
Yan	F	63	280/100	III	2 weeks	275/100	Neg.
Sil	F	23	170/110	IV	2 weeks	155/115	I
Swa	M	31	180/100	II	2 weeks	145/75	Neg.
Pea	M	35	190/110	I	2 weeks	125/75	Neg.
Goo	F	34	235/135	III	2 weeks	180/115	Neg.
Fie	M	32	170/110	II	2 weeks	135/85	Neg.
Bus	M	26	230/130	IV	2 weeks	165/95	Neg.
Fos	M	51	230/130	II	2 weeks	220/120	Neg.
Wat	M	50	215/120	I	2 weeks	150/90	Neg.
Pit	F	53	255/125	II	2 weeks	210/110	Neg.
Kon	M	50	205/110	III	2 weeks	165/90	Neg.
Nas	M	42	140/90	IV	2 weeks	140/75	Neg.
McCl	F	50	230/120	II	2 weeks	210/120	Neg.
Hur	M	21	220/125	II	2 weeks	180/110	I
Gol	M	31	230/135	II	2 months	240/145	Neg.
She	M	51	205/120 (s)		5 months	155/95	I
Dea	M	54	200/110 (s)		6 months	195/100	I
Yof	F	42	185/110 (s)		1 year	165/100	II
Bar	F	52	200/100 (s)		2 years	200/90	Neg.
Abe	F	35	185/130 (s)		2½ years	225/125	I
Dow	M	44	195/120 (s)		3 years	220/120	I
Ret	M	41	185/120 (s)		3 years	220/130	Neg.
Cha	F	37	165/100 (s)		4 years	135/75	I
Dem	M	52	225/125 (s)		4 years	230/110	Neg.
Lyn	M	42	175/130 (s)		4½ years	145/90	II
Sul	M	52	210/140 (s)		6 years	175/120	Neg.
O'L	F	47	140/90 to (s) 180/120		9 years	145/85	I

(s) As reported, taken with sphygmomanometer.

any way. When tested, the patient was found to have grade II, or definite, overshoots after the vasopressor stimuli (figure 6). Upon reoperation it was discovered that the scar tissue of the previous wounds did not extend to the sympathetic chains, which were fully intact. A routine lumbodorsal splanchnicectomy was therefore performed, whereupon the overshoot responses to the same stimuli became negative. It was also interesting and helpful to observe in patients studied years after extensive resection of sympathetic nerves supplying the splanchnic region that the vasopressor overshoots were absent or of a low order as compared with those in unoperated hypertensive patients, although they were somewhat greater than those found early after splanchnicectomy.

The degree of vasopressor reactivity present before, or remaining after,

sympathectomy could not be directly correlated with the level of basal arterial pressure. This reactivity might be slight in preoperative, or completely negative in postoperative patients with fixed high basal arterial pressures; and it might be of the most marked type in normotensive individuals, or in unoperated hypertensive patients with only moderately elevated basal arterial pressures.<sup>6, 7</sup>

## DISCUSSION

Since there are no consistent changes in cardiac output after sympathectomy such changes obviously do not explain any fall or lack of fall, in basal arterial pressure that may occur. Thus, it cannot be argued that a post-operative reduction of pressure is caused by a depressed cardiac output due to inadequate venous return.<sup>19</sup> Nor can it be said that a lack of fall of arterial pressure is caused by a compensatory rise in cardiac output in response to a decrease in peripheral resistance.

Furthermore, if there is a considerable change in blood flow in any peripheral area after sympathectomy, it must be offset by an opposite change in some other area or cardiac output would not remain the same. But, since no great change in blood flow has been found in any organ; even the liver, when arterial pressure has been lowered and become stabilized after sympathectomy, one must assume that there has been a widespread decrease in peripheral resistance to account for the lowering of pressure. Even when there is a large increase in blood flow through the liver with no fall in arterial pressure shortly after sympathectomy, the total peripheral resistance must be nicely adjusted, since cardiac output is unchanged. Such adjustments suggest a high order of integration of the total peripheral blood flow (represented measurably by the cardiac output), whether or not the arterial pressure is lowered after sympathectomy.

Investigators who have studied renal hemodynamics by clearance methods in hypertensive patients<sup>8, 10, 20, 21, 22, 23, 24</sup> seem agreed that there are no significant changes in renal blood flow following splanchnicectomy. Therefore, they have found it difficult to attribute any fall in arterial pressure that may occur after such operations to a change in the *effective renal circulation*. There remains a possibility that the renal extraction of the clearance substances used in these studies may not be the same before and after sympathectomy, so that calculations based upon an assumed unchanged extraction may not represent accurately the *total renal hemodynamics*.<sup>25</sup> This possibility is now under study in this laboratory.<sup>26</sup>

It may be argued that if renal blood flow is maintained when arterial pressure is lowered after sympathectomy, it is because of "autonomous" adjustments<sup>27</sup> in the renal vasculature resulting in a decrease in renal resistance.<sup>28</sup> Thus, an undiminished renal blood flow would simply represent an adaptive response to, and in no sense a cause of, the reduction in arterial pressure. But from the data so far available it may be argued with equal

logic that arterial pressure may be reduced after sympathectomy, if, despite this reduction, renal blood flow can be maintained by means of a release of renal arteriolar constriction,<sup>29</sup> presumably by the sympathectomy. In this view the reduction in arterial pressure would be contingent upon an undiminished renal blood flow. The two arguments differ not only in their relative emphasis upon renal blood flow and renal resistance,<sup>30</sup> but also in their implications as to the cause-and-effect relationships of these two factors and the arterial pressure. Certainly the whole matter is still open to question, and for that reason it is now being reviewed in this laboratory.<sup>28</sup>

Contrary to the results in the kidney, the findings reported here on blood flow through the liver have demonstrated a definite hepatic-portal vasodilatation to occur early after sympathectomy, whether or not the arterial pressure is lowered. As time goes on this vasodilatation seems to subside. Therefore, it is difficult to explain any change, or lack of change, in arterial pressure as due directly to hepatic-portal vasodilatation. Possibly in some patients it may furnish a more adequate supply of oxygen and/or other materials for hepatic (or other splanchnic visceral) metabolism and so indirectly affect the production or alteration of substances involved in the elevation of arterial pressure.<sup>31</sup> This possibility also is now being investigated by studying the hepatic-portal consumption of oxygen, conjugation of para-amino hippuric acid, and extraction of mannitol and other substances from the blood.<sup>32</sup>

The great reduction, or abolition, by sympathectomy of splanchnic vasoconstrictor responses to stimuli like the upright position may be of even greater importance than the increase in resting hepatic blood flow per se, since apparently it persists after the increase in hepatic blood flow has subsided. Again, however, such vasodilatation (or absence of vasoconstriction) in the upright, as in the horizontal position, cannot be accepted as the direct explanation for any lowering of basal arterial pressure that may develop after sympathectomy, since it is found even when the arterial pressure remains elevated.

Likewise, reduction or abolition of reflex vasopressor overshoots of arterial pressure after blood-pressure-lowering procedures and their substitution by a more stable, or gradual, homeostatic mechanism may be a very important hemodynamic effect of sympathectomy. Before operation, even in response to the relatively mild stimuli used, peaks of arterial pressure in excess of 300 mm. Hg were frequently reached in some patients. Though of brief duration they conceivably could cause vascular rupture or other serious damage. Therefore, in such hypertensive patients, especially those with high levels of basal arterial pressure, it may be advisable to abolish these overshoots even when the basal levels of arterial pressure cannot be changed by surgical intervention. Indeed, the symptomatic improvement in many patients who have had no significant lowering of basal arterial pressure after sympathectomy may be due to the amelioration of this type of vascular strain.

Comparative measurements of overshoot responses to blood-pressure-

lowering procedures pre- and postoperatively in the same patient have furnished assays of sympathetic vasopressor activity that thus far have correlated well with the type and extent of the operation performed. Whether they will also correlate with other estimates of sympathetic vasopressor activity that may be used to predict the effectiveness of surgical sympathectomy in different patients remains to be seen. Already they have proved to be of positive value in the sense that when the overshoots were marked, a large portion, if not all, of the splanchnic sympathetic nerve supply was found intact at operation, and if extensively removed resulted in the disappearance or great reduction of the overshoots. Furthermore, completely negative responses have as yet been obtained only in sympathectomized subjects. However, small (grade I) preoperative responses have been recorded occasionally in hypertensive patients in whom apparently normal sympathetic nerves were found at operation.

It seems fair to conclude that none of the direct hemodynamic effects so far discovered in the sympathectomized areas of hypertensive patients adequately explains the effectiveness of the operation in lowering the basal arterial pressure in some individuals, as contrasted with its failure in others. For, while the sympathetic nervous system seems obviously involved in the hypertension of some patients, since the removal of large parts of it results in a lowering of the pressure, in other patients indistinguishable from these preoperatively by the methods now at hand, the sympathetic nervous system seems at the time of operation as obviously not the dominant factor, since its removal causes little or no change in pressure. But in both groups the purely hemodynamic effects (except upon overall peripheral resistance) are similar and are not sufficient in themselves to account for any change in pressure that may occur. Therefore, the *direct hemodynamic effects* of sympathectomy appear to be non-specific, but it is entirely possible that in some patients these changes may act through *indirect physical or chemical mechanisms* to lower the basal arterial pressure some months later, if not immediately after operation.

These considerations, and others derived from collateral studies on the effects of hypotensive drugs in hypertensive patients<sup>33, 34, 35, 36, 37, 38</sup> have led to the working hypothesis in this laboratory that the elevated basal arterial pressure of hypertensive patients is regulated by an intricate and highly integrated mechanism that is probably controlled through the central nervous system. It seems possible that essential hypertension may result from a varied succession of events—psychological, neurological, metabolic, humoral and/or physical—that tend, at first intermittently, and later continuously, to raise the arterial pressure. Eventually, perhaps as an adaptive process, the central integrating mechanism controlling the basal arterial pressure may become set at a higher level, establishing a sort of vicious circle. Furthermore, it is possible that the number of inciting and/or perpetuating factors may increase or decrease as time goes on, so that in some patients only one, while in others a combination of them, may be acting to sustain the

elevation of arterial pressure. Therefore, in order to lower the pressure in some patients it may be necessary to correct only one of these factors, while in others it may require a number of different therapeutic procedures applied successively or simultaneously.

Such a concept, rather than a unitarian theory, seems to satisfy the known facts concerning the nature and the relief of essential hypertension in man. Thus, sympathectomy alone will correct the hypertension in some patients. Likewise, a salt-free diet will lower the pressure in others. However, it now appears that these two procedures together are more apt to lower the pressure than either one used alone.<sup>39</sup> Similarly, each of the fundamentally different drugs, *veratrum viride*<sup>33</sup> and *dihydroergocornine*,<sup>34</sup> used alone may lower the pressure in certain hypertensive patients; but together they will lower the pressure in selected patients that neither one alone will affect.<sup>38</sup> Finally, three or even all four of the treatments mentioned above have been used simultaneously with success in a few patients who had failed to respond satisfactorily to any other single or combined form of therapy.

While such results may be explained as due simply to the additive effects of several non-specific hypotensive procedures and agents, they may denote the multiform nature of the hypertensive disease in some patients. For, when there is a significant and persistent lowering of the basal arterial pressure unaccompanied by signs of collapse or by toxic or unphysiologic side reactions, it may be postulated that the central integrating mechanism for regulating the arterial pressure has been reset at a lower level. Whatever the explanation, it has seemed most worthwhile to persist in trials of single agent or combination therapy in such patients because the palliative results, measured by objective criteria, so far observed have been highly gratifying, even in some of the most severe and chronic of cases. Even if "symptomatic," such therapy is warranted until it is definitely known whether essential hypertension is a single disease or merely a manifestation of several different diseases, until the inciting causes and perpetuating mechanisms in every type of case are understood, and until effective specific methods of treatment are freely available. These things will come only through continued research.

### SUMMARY

Laboratory studies of the hemodynamic effects of sympathectomy in hypertensive patients have revealed (1) little change in basal cardiac output (direct Fick method), (2) an early increase and later moderation in hepatic-portal blood flow (BSP method), (3) a decrease in the splanchnic vasoconstrictor response to the upright position, and (4) a decrease or abolition of vasopressor overshoots of arterial pressure after depressor procedures. The postoperative effects are similar whether or not arterial pressure is lowered, except that hepatic-portal blood flow apparently is influenced directly by the level of the arterial pressure.

These results, along with the reported studies on renal blood flow, in-

dicating that the direct hemodynamic effects of splanchnicectomy do not account for any lowering of arterial pressure that may occur. However, it is entirely possible that in some patients indirect physical or chemical mechanisms resulting from these hemodynamic effects may in time act to cause a widespread decrease in peripheral resistance and a lowering of arterial pressure.

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# RESULTS OF HIGH DORSOLUMBAR SYMPATHECTOMY FOR HYPERTENSION \*

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It has been the custom at the Lahey Clinic for the medical department to choose and recommend certain hypertensive patients for dorsolumbar sympathectomy as well as to follow their postoperative and subsequent course. This report is an attempt on our part to evaluate the results of operation in a strictly critical and unbiased manner based upon a six month to three year follow-up on 173 patients who had sympathectomies to include the fourth thoracic level.

Our first series of 54 cases in which resection was carried out to the eleventh or twelfth thoracic level, reviewed by E. C. Bartels<sup>1</sup> in 1942, showed that only 37 per cent of patients with hemorrhagic ocular fundi and moderately fixed blood pressure (Keith-Wagener Group III) were benefited. His experience led him to evolve a set of very strict criteria for selection of cases for operation, so much so that the criteria were criticized on the basis that such patients should have a good prognosis for at least the five-year reported period, and that perhaps surgery was not justified in many of the mild cases. The patients in Group III with hemorrhagic fundi, 80 per cent of whose life expectancy will not exceed four years (Keith and Wagener), were thus left hopeless (figure 1). In an attempt to benefit this group of

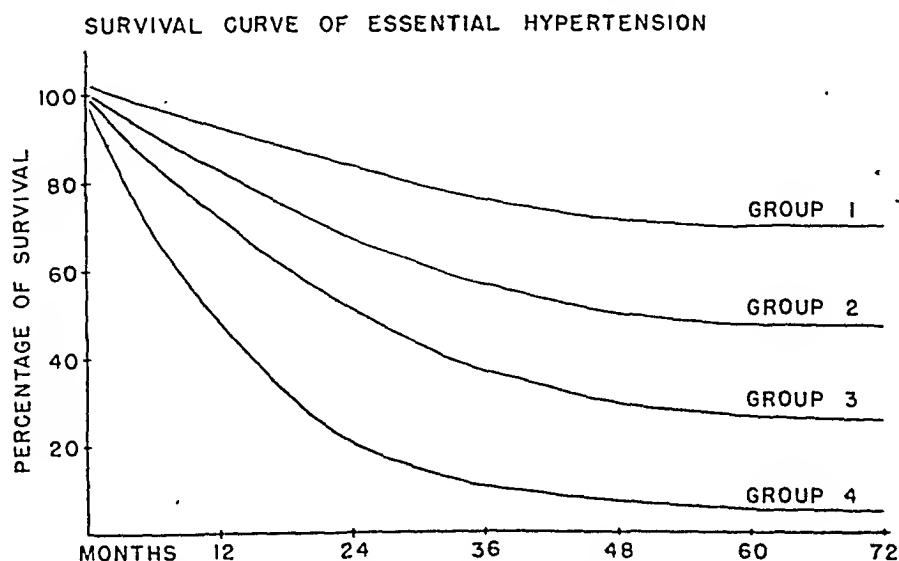


FIG. 1. Survival curve of essential hypertension (Keith, Wagener and Barker).

\* Read at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 23, 1948.  
From the Lahey Clinic.

patients and those in Group II with moderate cardiovascular renal changes whom we had been rejecting, sympathectomy was gradually raised from the twelfth thoracic to the third or fourth thoracic ganglion (figures 2 and 3). Popen, who performed these operations, reported his results during this gradual rise in 1947.<sup>2</sup> Good and fair results in Grade III patients rose from 37 per cent to 63 per cent in a group whose operations ranged in extent from the eleventh thoracic to the fourth thoracic ganglion.

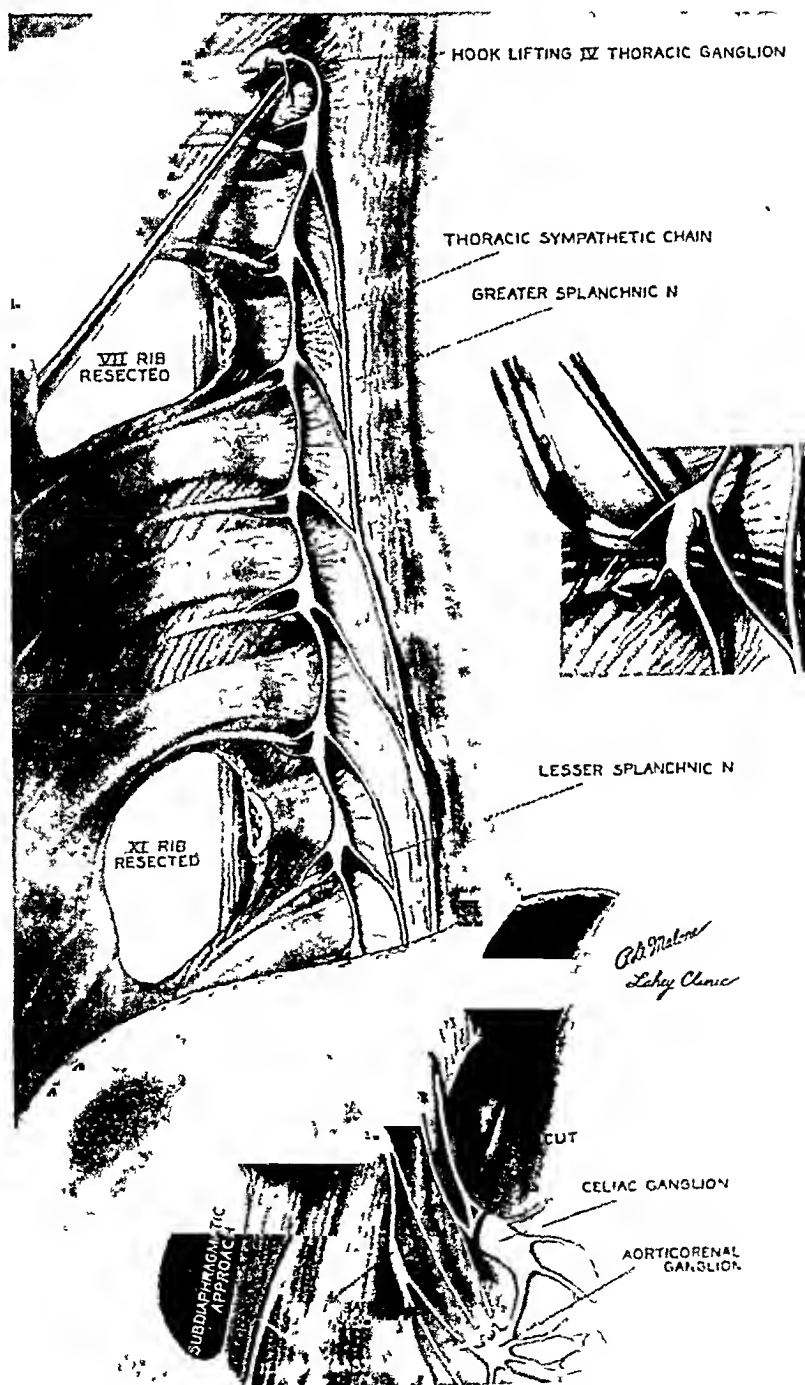


FIG. 2. The Popen dorsolumbar sympathectomy and splanchnicectomy for hypertension

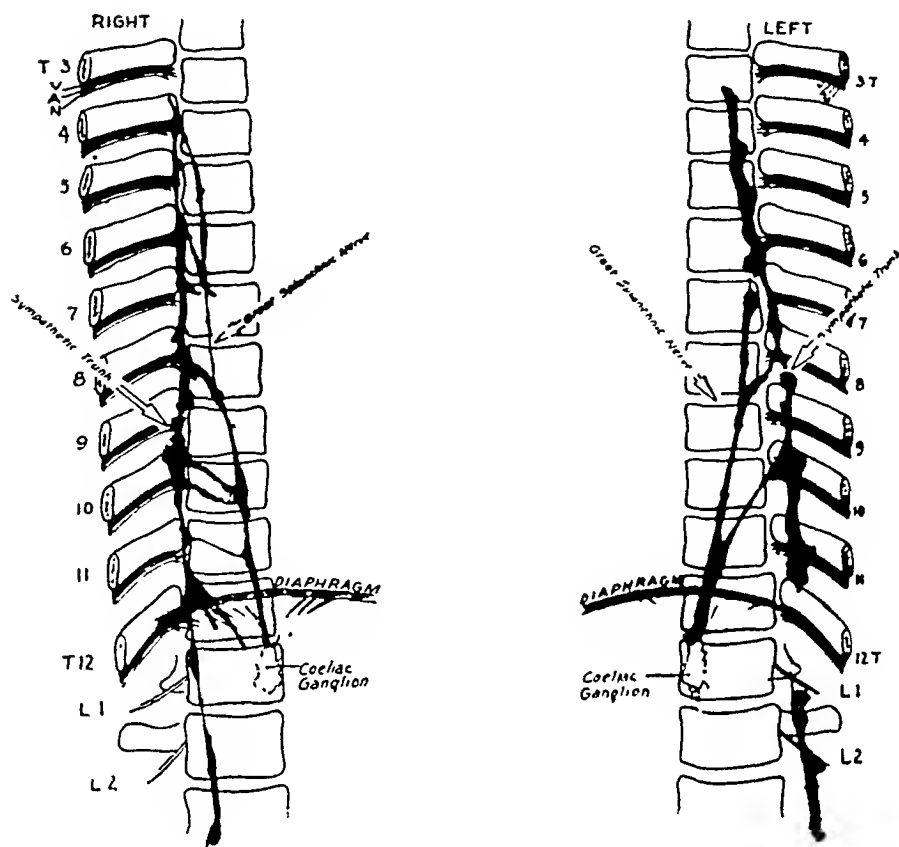


FIG. 3. Surgical specimens superimposed on drawing.

Experience with three patients with recurrent hypertension who had a second operation has supported us in our decision to raise the level of sympathetic resection. Branches to the splanchnic nerves always arise from the seventh thoracic and sometimes from as high as the third thoracic ganglions. Although the greater and lesser splanchnic nerves were cut at the level of the diaphragm in the seventh or twelfth thoracic to the third lumbar type of operation, these branches were found to have grown down again, reforming an amputation neuroma at the site of the celiac ganglion in all three cases (figure 4). In one case the growth was found to surround a silver clip left at the previous operation. The first operation had been at the level of the twelfth, eighth and seventh thoracic ganglions, seven, five and four years before, respectively. Sweat tests (figure 5) showed the sympathetics to the leg had not regenerated. Reoperation resulted in further drop in blood pressure in two patients. This led us to conclude that the splanchnic nerves constitute the most important area to be resected for decrease in blood pressure. A recent report from Smithwick's<sup>3</sup> group supports this contention.

It is difficult to test for splanchnic regeneration. Theoretically, there should be absence of abdominal visceral pain following splanchnicectomy, but only recently two patients have exhibited severe abdominal pain within



FIG. 4. Left, normal sympathetic ganglion and fibers. Right, amputation neuroma at site of celiac ganglion resected four years previously.

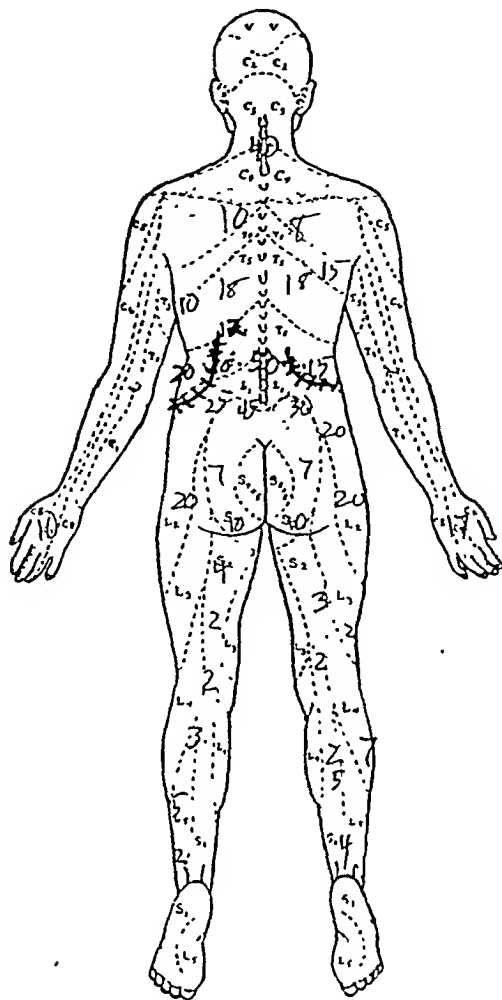


FIG. 5. Sweat test. This patient had a resection to the twelfth thoracic ganglion only, seven years before reoperation and the splanchnics cut at the celiac ganglion. The low figures show the minute current transmitted by the dry resistant skin in the legs which remain sympathectomized, yet the splanchnics were found regenerated at operation.

a few days after operation, one from gall-bladder disease and the other from an irritable spastic colon, without any sign of peritoneal irritation to account for the pain. Studies are being carried out with balloon distention of the gut and in one patient in whom this test was made no pain was experienced, yet at reoperation regeneration of the splanchnic nerves was found. Such regrowth of the thoracic sources of the splanchnics down into the celiac area, however, is only suggestive evidence of the necessity of resecting the splanchnics to their point of transit through the thoracic ganglions. We have no histologic or physiologic proof as yet that these new preganglionic fibers have actually established synapses in the celiac ganglion and are again functioning.

It must be stated *a priori* from our point of view as internists that we cannot accept six month to three year follow-ups in a chronic disease such as hypertension with any notion of forming reliable conclusions. To promise a patient of 30 with hypertension that he will live to the age of 70, an ex-

panse of 40 years, is as yet absurd. We are not even in a position to predict that patients with Grade III hypertension will exceed the 20 per cent expectation of surviving four years. All we can hope is that the observed reversal of retinal arterial changes toward normal, the frequent reduction in heart size and the improvement of kidney function should prolong life. We must wait 20 years for data in Group II cases, and 10 years in Group III cases to demonstrate that this procedure will check cardiovascular renal degenerative disease. In this regard Palmer<sup>4</sup> has stated there is a law of diminishing returns the longer the follow-up, from two thirds good results at the end of one year to 25 per cent at the end of three years, including all grades of hypertension. He also stated that a comparative group of 100 patients treated medically over three years had only half the number of good results.

High dorsolumbar sympathectomy has led us to reverse our criteria for the selection of patients. Formerly, we only thought, "Is this case mild enough with little enough cardiovascular degeneration to promise a good result?" The former operation was a comparatively less formidable procedure, possible, as Peet does it, in one stage, and required a comparatively short convalescent period of one to three months. Our present operative procedure has not resulted in raising the operative mortality rate. Three and a half to five weeks' hospitalization for a two-stage operation is necessary. Full economic recovery has required an average of five and a half months' convalescence for those patients now back at work. Nineteen patients were not back at work after one year. Much pain may be experienced for two to four months.

The main effect on the blood pressure is a profound orthostatic hypotension. In the first six months we have often substituted only one disease for another, namely, orthostatic hypotension for hypertension. This hypotension routinely requires a special corset with a spring suprapubic pad and elastic leg support (figure 6). In 19 cases we have had to resort to special pneumatic leggings patterned after the G-suit\* of our aviators (figure 7). This device has enabled such patients to return immediately to at least part time work and has been worn for periods of from one to three months, when they are able to discard it.

A profound drop of blood pressure after the second stage may lead to problems of reduced cerebral and coronary circulation in patients who have already had a cerebral or coronary thrombosis and requires extra efforts to maintain a higher blood pressure the first two days after operation. Our main reliance is on a constant flow of 1 per cent solution of neosynephrin in 5 per cent glucose and maintenance of shock position.† Another rare

\* The corset and G-suit are supplied by the Spencer Corset Company, to whom we are also indebted for the photographs.

† A note of warning is appended; two efforts to maintain a higher blood pressure level by pneumatic leggings led to temporary ischemic paralysis and foot drop when the systolic blood pressure fell to 80 mm., the level of air pressure found necessary to keep the suit inflated to raise the blood pressure 10 mm.

undesirable effect of this type of operation has been the appearance of Raynaud's phenomenon in the fingers of three patients. Palmer<sup>4</sup> has also reported such occurrences.

The prolonged and often extremely uncomfortable convalescence now makes us ask, "Is this patient's hypertension producing, or is it likely soon to produce, enough cardiovascular renal degeneration to justify such a serious operation? In the second place, are the changes already present irreversible?"



FIG. 6.

FIG. 7.

FIG. 6. Girdle with suprapubic spring pad worn for orthostatic hypotension after high dorsolumbar sympathectomy (Spencer Corset Company).

FIG. 7. Pneumatic leggings worn for severe hypotension following high dorsolumbar sympathectomy (Spencer Corset Company).

#### CRITERIA FOR HIGH DORSOLUMBAR SYMPATHECTOMY

Our criteria for selection of patients, since adopting the almost complete sympathectomy has, therefore, drastically changed in the past three years, and the purpose of this review is to determine whether results have justified operating on patients with more advanced hypertensive vascular disease.

Two courses were open to us: to operate on all patients with hypertension except the almost moribund, or to put a ceiling on our indications. Former experience during our period of gradually raising the level of sympathectomy and the reports of others in the field—Smithwick,<sup>5</sup> de Takats,<sup>6</sup> operating to levels as high as the ninth thoracic ganglion and Grimson<sup>7</sup> with a complete sympathectomy—made us choose the latter course. This policy has led us to set up a negative set of standards or certain criteria which if present would contraindicate operative procedures.

Parenthetically, the Wagener-Keith classification<sup>8</sup> of hypertension which we have used in previous reports from this clinic and are using again for the sake of comparison, may be reviewed.

Group I. Patients whose blood pressure drops to normal on rest with Grade I fundi, the earmark of which is increased light reflex only.

Group II. Patients whose blood pressure drops to normal or near normal on rest or sedation with sodium amytal. Fundi are Grade II, the earmark of which is compression at the arteriovenous crossings and often some spasm.

Group III. Patients whose blood pressure drops but little on rest or sedation; fundi, earmark of which is hemorrhage or exudate often with marked spasm.

Group IV. Patients with high blood pressure which does not drop on bed rest or sedation with sodium amytal. In the latter test, the diastolic pressure stays well above 100. Fundi are Grade IV, the earmark of which is choked disk or edema of the disk. There is also hemorrhage, exudate and fragmentation of the vessels.

It must be stated here that many patients with Grade III or IV fundi may have labile blood pressures, that is, the diastolic pressure will still drop below 100 mm. of mercury on sedation with sodium amytal or will drop after etamon to below 100 mm. in the supine position (etamon will cause an orthostatic hypotension in almost all patients with any grade of hypertension and by experience such an orthostatic hypotension indicates nothing).

Our cases are tabulated according to Wagener and Keith's classification based on fundi alone for the sake of simplification, and because earlier reports from this clinic have also been on this basis. Although Wagener and Keith required certain degrees of lability of blood pressure in order to classify cases in each of their four groups, practically, it is impossible to do so because a patient with Group IV fundi may have Group I lability. A reclassification, therefore, along the lines suggested by de Takats,<sup>6</sup> taking into account lability, vascular and visceral damage, would seem more practical and satisfactory since results from all types of sympathectomy fall in line better with such a regrouping. For instance, a patient with Grade III or occasionally even Grade IV fundi may have a good result if the blood pressure is still labile, and renal, cardiac and vascular damage is still moderate. All 10 of de Takats' patients in Group III died, nine within one year, whereas many patients with Grade III fundi have good results.



What we have termed our negative criteria for operation are as follows:

(1) We rarely operate immediately on patients with Grade I fundi and with blood pressures that fall to normal on rest in patients of any age. We prefer to follow their course for a few years and attempt psychotherapy in the neuropsychiatric department, in most of the young patients. We believe that many of these patients have benign hypertension and will tolerate their labile blood pressure well for a normal life span. If under observation their basal resting diastolic pressure is consistently found to be above 100 mm. or signs of vascular or cardiorenal damage develop, we advise operation.

(2) We rarely accept patients over 50 years of age but have operated upon a few between 50 and 57 years of age if they still had a labile blood pressure, did not show evidence of arteriosclerosis or did not have Grade IV fundi. By labile blood pressure we mean a diastolic pressure that will fall below 100 mm. of mercury after administration of sodium amytal and below 100 mm. in the supine position after giving 3 c.c. of etamon intravenously. Our search for arteriosclerosis includes roentgenograms for calcification of the cerebral arteries as well as evidence of calcification in the aortic arch in the routine seven foot chest plate, of the pelvic arteries in the intravenous pyelogram, and often a roentgenogram with soft technic for the arteries in the leg. The presence of arcus senilis and palpably hardened peripheral arteries is included in the vascular survey.

(3) We reject patients with long-standing hypertension who have reached the age of 50 and who seem to be tolerating their hypertension well; in other words, their renal function is still good, their hearts are not enlarged and they have only Grade I or II fundi. These patients probably will live as long without operation as with it.

(4) Patients are refused surgery who have marked hemiplegic residual symptoms in whom operation would hardly be worth while on account of marked hemiplegic crippling effect. Minor cerebrovascular accidents from which the patient has largely recovered do not by themselves contraindicate operation.

(5) No patient is accepted who has severe right side congestive failure, but those who have experienced episodes of nocturnal dyspnea (pure left ventricular failure) are not considered to have a contraindication if renal function is good and the blood pressure labile.

(6) We reject patients who have any severe degree of coronary insufficiency or who have had coronary infarction. The existence of mild angina pectoris with normal exercise tolerance tests, a normal sized heart, and without much dyspnea on exertion, or angina pectoris with a large neurogenic factor does not contraindicate operation. Indeed, a patient with such findings is now subjected to a sympathectomy to the stellate ganglion level to include the anginal pathway.

(7) We do not accept patients with poor renal function, especially if the nonprotein nitrogen remains over 40 mg. per 100 c.c. or if the intravenous

pyelogram shows inadequate concentration of the dye. Poor concentration on the Fishberg test, poor phenolsulfonphthalein excretion, albumin in the urine, poor urea clearance, and a few casts or red blood cells in the urine should not individually rule out a candidate. A combination of such poor tests, however, points to such renal damage that it may be considered irreversible and the patient rejected for operation.

(8) We carefully screen out the following: glomerulonephritis, coarctation of the aorta, polycystic kidneys, pheochromocytoma, brain tumors, endocrine disease such as Cushing's syndrome, the systolic hypertension of arteriosclerosis and patients with unilateral Goldblatt's kidney. In the case of Goldblatt's kidney it has been our policy to do a splanchnicectomy on the same side as we do a nephrectomy. We then wait to see whether there is a secondary rise of blood pressure after this first stage splanchnicectomy. If there is, splanchnicectomy on the other side is carried out. If there is not a rise of the blood pressure after the first stage splanchnicectomy, we attribute the hypertension to the Goldblatt's kidney and do not complete the splanchnicectomy.

(9) Finally, we reject the patient with Grade IV fundi if he has a fixed blood pressure with or without the usual widespread cerebrocardiorenal disease.

The positive indications for operation are:

(1) We urge operation on patients with Group II fundi and labile blood pressure, believing that we get good results in 73 per cent. We especially recommend operation if there are signs of degenerative cardiovascular or renal disease which we believe are still reversible. This may include individuals with an enlarged heart but without a history of congestive failure. If there is evidence only of early renal sclerosis with albumin in the urine, some limitation of concentration function and nocturia, they are accepted for operation. Albumin and nocturia will often disappear after splanchnicectomy. In this group, too, we believe that spasm and compression in the fundi constitute a positive indication for operation rather than a contraindication, providing the blood pressure is still labile and there is no advanced arteriosclerosis.

(2) We operate on many patients with Group III or IV fundi if there is a fair degree of lability of blood pressure and none of the cardiovascular renal contraindications stated under "negative criteria." We inform the patient and family that if he does not have an operation, the four-year survival rate is 20 per cent. If he is operated on, the four-year survival rate may be 50 per cent. Do they want to take a chance with nature or with surgery? If the family understands the situation, operation is performed. Of course, it is in this group that the operation earns ill repute. We cannot deny splanchnicectomy to the 36 per cent of these patients who will have good results plus 41 per cent of patients who will have fair results.

(3) We also include patients for operation who have chronic pyelonephritis with hypertension whose nonprotein nitrogen is not elevated and whose intravenous pyelograms still show fair power of concentration. An added requirement for the treatment of chronic pyelonephritis is to sterilize the patient's urine before operation.

## RESULTS

The results tabulated are for a follow-up period of six to 33 months, average 11 months. In computing our results we have compared in table 1 the patient's first "off-the-street" blood pressure reading with an "off-the-street" supine blood pressure reading after operation at the last follow-up visit. To rank the result on supine blood pressure as excellent we have required a normal blood pressure. To rate the result as good, there must have been a fall of 50 mm. systolic and 20 mm. diastolic, and the blood pressure must have fallen below 200 mm. systolic and 120 mm. diastolic. To rank the result as fair, the systolic must have dropped 30 mm. and the diastolic 10 mm., but the blood pressure is above 150 mm. systolic and 100 mm. diastolic. The blood pressure drops of 10 patients who died several months after operation are included in these tables on supine and standing blood pressure.

TABLE I  
Results of High Dorsolumbar Sympathectomy on Supine Blood Pressure

	Group I	Group II	Group III	Group IV	Total
Excellent	3	31	5	0	39
Good	3	29	9	1	42
Fair	1	19	11	2	33
Poor	1	32	20	6	59
Total	8	111	45	9	173

Summary of Results on Supine Blood Pressure

	Groups I and II	Group III	Group IV	Total
Excellent or good	55.5%	31.0%	11.0%	46.8%
Fair	16.8%	24.5%	22.2%	19.0%
Poor	27.7%	44.4%	66.6%	34.1%

We have also compared the "off-the-street" blood pressure of the patient's first visit with the standing blood pressure of the final follow-up visit (table 2). This comparison, naturally, yields the most impressive results. We have been especially interested in the marked orthostatic hypotension produced by this extensive operation since it is believed to cause a redistribution of circulating blood volume responsible for the relief of symptoms and cardio-

vascular improvement. If the patients live longer following splanchnicectomy it is probably because such an orthostatic hypotension has been brought about. Furthermore, the high supine blood pressure recorded in the physician's office may not be that of the patient when he is asleep supine. In other words, the average blood pressure the clock around is bound to be much lower in the patients who have obtained a good orthostatic hypotensive result.

TABLE II  
Results of High Dorsolumbar Sympathectomy on Orthostatic Blood Pressure

	Group I	Group II	Group III	Group IV	Total
Excellent	6	62	15	2	85
Good	0	14	7	1	22
Fair	2	23	11	2	38
Poor	0	10*	10	4	24
No report		2	2		4
Total	8	111	45	9	173

\* 1 operative death.

Summary of Results on Orthostatic Blood Pressure

	Groups I and II	Group III	Group IV	Total
Excellent or good	69.0%	48.8%	33.3%	62.0%
Fair	21.0%	24.4%	22.2%	22.0%
Poor	8.4%	22.2%	44.4%	13.8%
No report	1.0%	4.4%		2.3%

In the table for orthostatic effect on blood pressure after sympathectomy, excellent means a blood pressure after one minute or more in the standing position, not exceeding 150 mm. systolic and 100 mm. diastolic; good means an orthostatic blood pressure above 150 mm. systolic and 100 mm. diastolic, with a marked drop compared with the "off-the-street" blood pressure before operation. For a fair rating there has been only a moderate drop in blood pressure but a standing pressure below 200 mm. systolic and 120 mm. diastolic. A rank of poor means the standing blood pressure is still above 200 mm. systolic and 120 mm. diastolic, or with no or very little drop (table 2).

#### COMMENT ON RESULTS ON SUPINE AND ORTHOSTATIC BLOOD PRESSURE

From a review of tables 1 and 2 it is apparent how frequently a good orthostatic drop in blood pressure is obtained and how disappointing the effect on the supine blood pressure may remain. Only 34 out of 119 patients with

Groups I and II fundi had normal postoperative blood pressure when lying down, but 68, or more than one half, had normal blood pressures when standing up. Only one-ninth of the patients with Group III fundi had normal supine blood pressures following operation, but one-third had a normal blood pressure when erect. About a fourth of patients with Groups I and II fundi had poor results on supine blood pressure, but only 8.4 per cent had a poor result on their erect blood pressure. In Group III, 44 per cent of the patients had poor results on supine blood pressure and 22 per cent when the patient was standing. Of the entire series of 169 patients, on whom there is a report on the standing blood pressure, only 24 or 14 per cent failed to obtain at least a moderate drop of their blood pressure when they were erect.

### SYMPTOMATIC IMPROVEMENT, ECONOMIC STATUS AND "TOTAL SCORE"

In arranging our statistical tables for symptoms and economic status (tables 3, 4 and 5) we tried to avoid the old cliché that one can prove anything by statistics and looked at the results from the viewpoint of both the patient and his referring physician. Our criteria for scoring in tables 3, 4 and 5 are as follows:

TABLE III  
Relief of Symptoms after High Dorsolumbar Sympathectomy

	Group I	Group II	Group III	Group IV	Total
Excellent	0	9	1	0	10
Good	5	69	25	1	100
Fair	3	14	11	2	30
Poor	0	6*	4*	6*	16†
No report		13	4		17
Total	8	111	45	9	173

\* 4 deaths.

† 12 deaths.

### Summary of Results on Symptoms

	Groups I and II	Group III	Group IV	Total
Excellent or good	69.7%*	57.7%*	11.1%	63.5%
Fair	14.3%	24.4%	22.2%	17.3%
Poor	5.0%†	8.9%†	66.6%†*	9.2†
No report	11.0%	8.9%		9.9%
Total	100%	99.9%	99.9%	99.9%

\* 78% of those patients reporting.

† 4 deaths.

‡ 12 deaths.

TABLE IV  
Economic Status after High Dorsolumbar Sympathectomy

	Group I	Group II	Group III	Group IV	Total
Excellent (100% at 3 mos.)	1	17	2	0	20
Good (100% at 6 mos.)	1	40	14	1	56
Fair (75% at 6 mos.; 100% at 1 yr.)	2	16	5	2	25
Poor (not working)	1	4*	8*	6*	19**
No report	3	34	16		53
Total	8	111	45	9	173

\* 4 deaths.

\*\* 12 deaths.

Summary of Economic Status

	Groups I and II	Group III	Group IV	Total
Excellent or good	49.5%	35.5%	11.1%	44.0%
Fair	15.1%	11.1%	22.2%	14.4%
Poor	4.2%	17.7%	66.6%	11.0%
No report	31.1%	35.5%		30.6%

TABLE V  
Total Score

	Group I	Group II	Group III	Group IV	Total
Excellent	0	4	0	0	4
Good	7	77	20	1	105
Fair	1	19	19	3	42
Poor	0	8	6	5	19
Insufficient data		3			3
Total	8	111	45	9	173

Summary of Total Score

	Groups I and II	Group III	Group IV	Total
Excellent or good	74.0%	44.4%	11.1%	63.0%
Fair	16.8%	42.2%	33.3%	24.2%
Poor	6.7%	13.3%	55.5%	11.0%
Insufficient data	2.5%			1.7%

Under symptoms, complete relief counted a score of excellent. Good means relief of all but one of the following symptoms: nervous tension, headache, dizziness, fatigue, plus a sense of well-being. Fair represents partial relief of all or most symptoms, or partial return of some symptom, usually headache. The 12 deaths in the entire series were counted poor as regards symptoms and economic status. Economic improvement is explained in the table.

The "total score" (table 5) was computed as follows: excellent in any of the categories counts four points toward a total of 16; good counts 3; fair counts 2; poor 1; no report 0. The count of 1 for poor was compensated for by raising the total requirements 1 point for each final category in the "total score."

A score of excellent in the "total score" requires 15 to 16 points; good 10 to 14 points; fair 7 to 9 points; any score below 7 rates poor. The 12 fatalities are rated poor. Thus one patient in Group III who had a good result in all four categories for a total score of 12, died from a sudden cerebral accident nine months after operation, but must naturally be counted a poor result.

#### COMMENT ON SYMPTOMATIC IMPROVEMENT, ECONOMIC STATUS AND "TOTAL SCORE"

Seventy-eight per cent of patients in Groups I and II and 63 per cent in Group III who reported symptoms on follow-up examination obtained marked relief, but in Group IV two-thirds of the patients failed to obtain relief or died (table 3).

Seventy-two per cent of patients reporting in Groups I and II were working full time six months after operation, 94 per cent by one year (table 4). Fifty-five per cent of patients reporting in Group III were working full time six months after operation, 74 per cent by one year. Eighty-four per cent of those reporting in the entire series were working full time by one year.

The good "total score" in Grades I and II (table 5) exceeds the good orthostatic blood pressure result by only 5 per cent, 74 per cent and 69 per cent, respectively. Only 29.1 per cent of patients in these two groups failed to obtain a good orthostatic fall of blood pressure. In patients with Group III fundi the good "total score" and good fall of orthostatic blood pressure were again parallel, 44.4 per cent and 48.8 per cent, respectively, and failure to get a good fall was 46.6 per cent. If one adds the percentage for total excellent and good score to the percentage of failure to get a good orthostatic drop in blood pressure, almost exactly 100 per cent of the patients are accounted for in Groups I, II and III. This substantiates our belief that the chief benefit of this operation is the redistribution of circulating blood volume.

Only 11 per cent of good results (table 5) in patients with Group IV fundi, and over one half poor results emphasize the importance of this contraindication to operation.

The results for 15 patients with Group II fundi would be raised from good to excellent on their total score if they had been able to resume full time work in three months instead of six. We have kept this strict criterion because it reflects the long convalescent period from this type of operation.

## EFFECT OF OPERATION ON VASCULAR AREAS

While decrease in blood pressure is certainly a desirable result, we doubt that it should be considered the only judge of the benefit of splanchnicectomy since even more startling benefits are often observed even when the fall in blood pressure has not always been satisfactory. Therefore, we have prepared tables showing improvement in areas of cardiovascular degeneration. Bridges et al.<sup>9</sup> have reported similar improvement in cardiac findings following dorsolumbar sympathectomy.

1. *Cerebral Vascular Area.* We believe with de Takats<sup>6</sup> and Smithwick<sup>3</sup> that the symptomatic and visceral improvement is due to redistribution of circulating blood with lowering of venous pressure and diminished diastolic cardiac filling, the effect of orthostatic hypotension. Previous experience before this series now reported, had taught us that if cardiac reserve has been too limited before operation, diminished diastolic filling may only tax the heart further and give rise to serious symptoms of forward failure. Reduced coronary irrigation may result in angina of serious coronary insufficiency. On the other hand, we have not observed any ill effects from reduced cerebral irrigation except immediately after operation, after both the first and second stages (table 6). There were two deaths in this series soon after operation from this cause, both in patients who had had no previous cerebrovascular accident.

TABLE VI  
Cerebrovascular Accidents

	Preoperatively	Postoperatively
Group I	1 0 in 7	0 0
Group II	9 0 in 101	1 4 (2 fatal at op.)
Group III	9 0 in 33	0 3 (2 fatal)
Group IV	1 0 in 7	0 1 (fatal)

Twenty patients had had cerebrovascular accidents prior to surgery, only one of whom had a subsequent nonfatal stroke. Of patients who never had had similar troubles, there were eight cerebrovascular accidents, varying in time from a few days to several months after operation, two of which were fatal. It would seem a previous cerebrovascular accident need not deter us from operating.

2. *Cardiac Vascular Area.* A. Angina (table 7). Nine of 15 patients with angina experienced abolition of pain and two partial relief. Angina remained the same in one, became worse in two, one of these patients dying of coronary infarction. Since one-third of our patients with angina did not



obtain complete relief, we feel supported in our present practice of resecting bilaterally the anginal pathway of the first, second, third and fourth thoracic ganglions. We did not operate on any patient with an electrocardiographic pattern of coronary infarct.

TABLE VII

## Angina

Group I				Group II				Group III				Group IV			
Be- fore	After	Left	Right	Before	After	Left	Right	Before	After	Left	Right	Be- fore	After	Left	Right
+	0	T-4	T-5	+	0	T-4	T-5	+	0	T-4	T-4	+	0	T-4	T-4
				+	++*	T-4	T-5*	++	+	T-4	T-4				
				0	+	T-4	T-4	+	+	T-4	T-4				
				+	0	T-4	T-4								
				++	0	T-5	T-4†								
				+	0	T-3	T-5								
				+	0	T-4	T-4								
				+	+	T-4	T-4								
				0	+	T-3	T-5								
				+	0	T-2	Stel- late								

\* Died of coronary infarction 12 months after operation.

† Died of auricular fibrillation 16 months after operation.

In the last series of cases reported from the Lahey Clinic by Poppen<sup>2</sup> there were eight patients with angina, in none of whom was resection carried to the fourth thoracic level. Only one patient obtained complete relief, two patients were better as regards angina, and five subsequently died. When operation was below the fourth thoracic level, there was 12.5 per cent relief; at the fourth thoracic level, 60.0 per cent relief, one patient undergoing resection to the second thoracic ganglion on the left and to the stellate ganglion on the right. It will be interesting to note what the results on angina will be when more patients are subjected to the still higher operation.

B. Heart size (table 8; figure 8). The hearts of 51 patients were reported preoperatively to have a transverse cardiac diameter greater than 50 per cent of the greatest transverse diameter of the chest. Twenty of these revealed normal ratios, many as soon as three to six months after operation; in eight the heart was reduced in size, two showed no change and in one the

TABLE VIII  
Change in Heart Size

	Cases
Enlarged before operation	51
Normal size 3 to 6 mos. after operation	20
Reduced but still enlarged	8
No change	2
Larger	1
Unreported	20

Reduction of size in 90%; 64% to normal

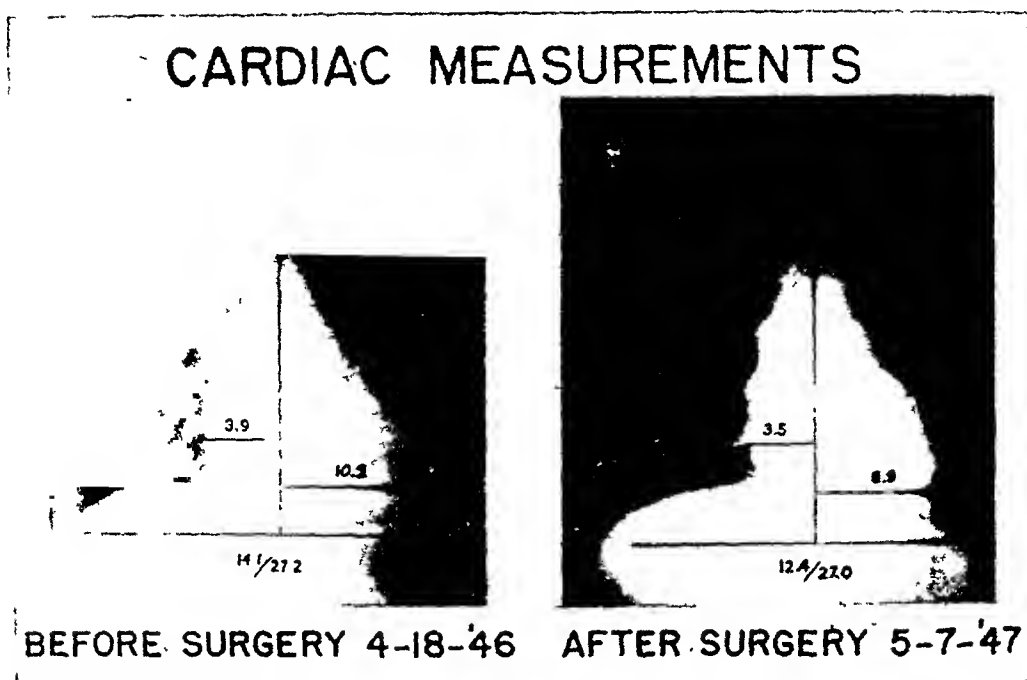


FIG. 8. Decrease in heart size to normal one year after sympathectomy.

heart was larger. There was no follow-up on heart size in 20 per cent. Of those with check-up examinations after operation, 90 per cent showed reduction in the transverse diameter of the heart, 64 per cent to normal.

C. Electrocardiogram (table 9; figure 9). Of a total of 173 patients the electrocardiograms were normal in 41 and abnormal in 92 before operation. Fifty of these latter patients had follow-up electrocardiograms after operation. Of these 50, 21 showed improvement (42 per cent), 28 no change and one was worse.

TABLE IX  
Electrocardiographic Data

	Left Axis Deviation Only					Left Ventricular Strain				Normal		
	Total	Improved	Same	Worse	No Report	Total	Improved	Same	No Report	Total	Same	No Report
Group I	1				1					6	1	5
Group II	27	2	8		17	28	11	7	12	30	6	24
Group III	16	0	11	1	3	19	8	2	9	3		3
Group IV						1			1	2	2	

D. Aorta. Of 11 patients who had widened, tortuous or calcified aortas, five had a total score of good, three of fair and three poor, making eight patients in whom the operation may have been worth while. In a few of these patients the aorta was noted to be less tortuous after operation.

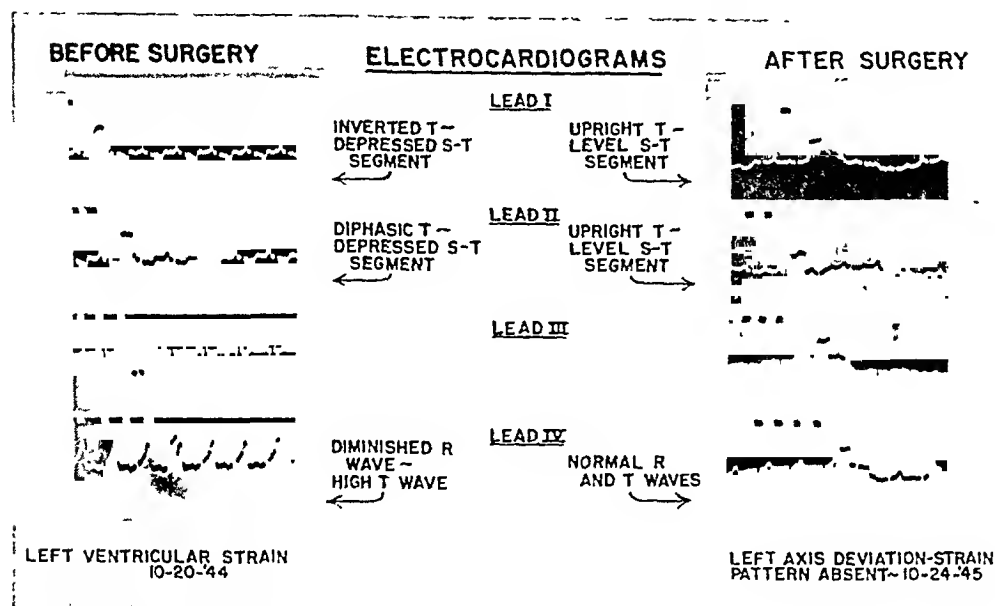


FIG. 9. Disappearance of left ventricular strain pattern one year after sympathectomy.

TABLE X  
Renal Function

	Nocturia	Improvement	Same	Worse
Group II	21	14	6	1
Group III	21	17	3	1
Group IV	3	3		

	Impaired	Improved in 1 or More Tests	Same	Worse
Group II (adequate comparative tests before and after operation)	36	21	12	3
Group III (adequate comparative tests before and after operation)	16	8	6	2
Group IV	3	3		

3. *Renal Area* (table 10). A. Nocturia was a symptom in 45 of the entire series of 173 patients. There was complete or partial relief in 34, or 75 per cent. Nocturia remained the same in nine and became worse in two.

B. Impaired renal functional tests were found in 55. After operation there was improvement in one or more tests in 32, or 58 per cent. The tests were practically the same in 18 and worse in 5. The tests included in this summary were for albumin, casts, Fishberg concentration tests, and often a phenolsulfonphthalein excretion and urea clearance test.

4. *Fundi* (table 11). A follow-up examination of the fundi was recorded in 117 patients in Grades II, III and IV. All fundi were graded by the senior author (J. A. E.). There was a reversion to normal in 12, in one of whom the fundi were originally Grade III. Thirty-seven of 73 who

TABLE XI  
Fundi

	Group II	Group III	Group IV
Reverted to I	37	6	2
Reverted to II		29	3
Reverted to III			1
Reverted to normal	11	1	
No change	25	2	
Advanced	0	0	0
Total	73	38	6

had Grade II fundi improved to Grade I, 25 showed no change; 38 with Grade III fundi were checked and 29 changed to II, six to I and there was no change in two. Of six patients with Grade IV fundi, one changed to III, three to II and two to I. It is to be noted that all Grade IV fundi improved. Two patients who were practically blind were able to read again one to two months following operation. No ocular fundi became worse after operation, although with the passage of time some Grade III fundi which improved for a while reverted to Grade III. These are included under no change.

## ANALYSIS OF DEATHS

There were 12 deaths in the entire series of 173 patients, a mortality of 7 per cent within a six to 33 month follow-up period. Two fatalities occurred before the patients had left the hospital, giving an operative mortality of 0.5 per cent (two operations were carried out on each patient). Both these figures are the same as in Poppen's last series of lower resections. Ten patients died five to eighteen months after operation, two of these 10 from coronary occlusion, three of cerebrovascular accident, and three of uremia. The cause of death is unknown in two (table 12).

TABLE XII  
Analysis of Deaths

	Total Deaths	Operative Mortality	Case Mortality			
		Cerebrovascular Accident	Coronary	Cerebrovascular Accident	Uremia	Cause Unknown
Group I	0	0				
Group II	4	1	2 { 18 mos. 15 mos.			13 mos.
Group III	4	0		2 { 11 mos. 10 mos.	7 mos.	12 mos.
Group IV	4	1		14 mos.	2 { 7 mos. 5 mos.	
Total	12					

Operative mortality, 0.5%.  
Mortality, 7%.

## GENERAL COMMENTS

Psychic relief has been a striking result in 60 per cent and fair in an additional 20 per cent of patients reporting release in varying degrees from nervous tension. Patients often volunteer such remarks as, "Things don't bother me like they used to," "Now I can sit and relax and not have to get up and go out." Whether this effect is psychologic or from cutting psychosomatic pathways is conjectural.

The average age of poor total score in patients with Groups II and III fundi was 42.5 years, of fair results was 41.1 years and of good results, 41.7 years. Therefore, in 156 patients none of whom were over 55 years, age seems to make no difference in results. This agrees with a statement by de Takats.<sup>10</sup> Patients with Group IV fundi have been left out of this consideration because malignant hypertensives average younger, yet have the poorest results.

It must be our next task to analyze our poor results and our best results in an attempt to reclassify our criteria for operation but we still believe it is too early to do so accurately since at least 100 patients with three-year follow-up studies are needed for a reliable opinion. High dorsolumbar or almost complete sympathectomy must justify itself on greater permanence of results since our main arguments for this operation are to resect a higher somatic sympathetic distribution and to prevent regeneration of the splanchnic nerves by creating a longer bed of scar tissue through which they must regrow.

In the category of patients with Group II fundi, Poppen in his series of

TABLE XIII

Comparison of Results of Last Reported Series of Cases from the Lahey Clinic with Resections to Various Levels Ranging from the Eleventh to the Fourth Thoracic Ganglions and the Present Series All to the Fourth Thoracic Level\*

	Groups I and II	Group III	Group IV
Good			
First series	39.0%	21.0%	4.0%
Second series	74.0%	44.4%	11.1%
Fair			
First series	16.0%	8.0%	0.0%
Second series	16.8%	42.2%	33.3%
Poor			
First series	23.0%	37.0%	56.0%
Second series	9.2%	13.3%	55.5%

## Summary of All Groups in Both Series

	First Series	Second Series
Good	47.0%	63.0%
Fair	24.0%	24.2%
Poor	22.0%	12.7%

\* Comparison is somewhat misleading because the earlier group was followed for one to four years, while the present group has been followed for only six months to three years.

lower operation reported from this clinic 23 per cent unsatisfactory results (table 13). We now report 6.7 per cent unsatisfactory on the basis of "total score," 9.2 per cent when cases with insufficient data are included, 8.4 per cent unsatisfactory from the viewpoint of erect blood pressure and 27.7 per cent unsatisfactory for supine blood pressure.

We regard the group of hypertensive patients with Grade III fundi as the real testing ground for high dorsolumbar sympathectomy, having designed the operation in the hope of better meeting their need than lower sympathetic resection had proved to do in our hands. With the lower operations on patients with Group III fundi, this clinic had 37 per cent unsatisfactory results; with the high resection to the fourth thoracic level, 13.3 per cent (table 13). The good results in this critical group in the earlier series were 21 per cent, in the present series 44.4 per cent based on "total score." We can only hope longevity figures 10 years from now will justify our expectation that we are salvaging a larger number of patients with severe hypertension by high dorsolumbar sympathectomy.

The evaluation of high dorsolumbar sympathectomy must await the test of time. Will taking the higher ganglions prevent regeneration of the splanchnic bed? It is also our belief that many patients will go on having sclerosing arteriolar disease whether or not there is regeneration of their splanchnic nerves. Other patients will continue to produce more and more pressor substance and many others will continue to be hyperkinetic, and slowly redevelop even orthostatic hypertension.

### SUMMARY AND CONCLUSIONS

This study of the results of high dorsolumbar sympathectomy from the fourth thoracic to the second or third lumbar ganglions, was undertaken in an attempt to ascertain whether a larger number of patients with all types of hypertension were being aided than by lower sympathetic resection in former series reported from this clinic. Special interest has been taken to determine whether more patients with Group III fundi (Keith-Wagener) may be salvaged. All the operations have been performed by one surgeon, Dr. James L. Poppen, except a very few recently by his associate, Dr. Kenneth E. Livingston. Although the present series has been followed a shorter time and doubtless with the passage of one or two more years the difference in figures will not be so marked (table 13), the superiority of results in patients with Group III fundi (hemorrhage and exudate) has doubled, from 21 to 44 per cent. Poor results have dropped one-third, from 37 to 13 per cent.

Good results in patients with Groups I and II fundi have almost doubled, from 39 to 74 per cent, and poor results are less than one half, having dropped from 23 to 9 per cent.

The principal effect of splanchnicectomy on hypertension is orthostatic, and evidence is reported that symptomatic relief is parallel to drop in orthostatic rather than supine blood pressure.

High dorsolumbar sympathectomy did not protect eight patients among the 173 in this series from subsequent cerebrovascular accident, two of them fatal.

Angina was wholly or partially relieved in 60 per cent of 15 patients, none of whom had serious coronary disease.

Ninety per cent of patients with abnormally wide transverse diameters of the heart showed reduction of heart size, 64 per cent to normal.

There was improvement in 42 per cent of 50 patients who had abnormal electrocardiograms.

Seventy-five per cent of 45 patients with nocturia reported complete or partial relief. At least one renal function test was improved in 58 per cent of 55 patients who had one or more impaired tests before operation.

Retinal vascular change improved in 66 per cent of 117 patients on whom follow-up examination was possible.

Operative mortality was 0.5 per cent; mortality rate for the entire series within the follow-up period of six to 33 months was 7 per cent.

We are loathe to consider this type of operation with its prolonged uncomfortable convalescence as a prophylactic operation for benign hypertension but urge it on patients under 50 years of age with spastic, exudative and hemorrhagic retinal arteriolar changes, moderate cardiac damage, signs of early nephrosclerosis, and labile blood pressure.

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# RETROGRADE ARTERIOGRAPHY IN THE DIAGNOSIS OF CARDIOVASCULAR LESIONS. I. VISUALIZATION OF ANEURYSMS AND PERIPHERAL ARTERIES\*

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RECENT advances in vascular surgery have created a demand for more accurate methods of diagnosis. Just as developments in surgery of the abdomen, urinary tract, head, and thorax have been aided by improvements in radiographic technic, so advances in vascular surgery may be expected to develop with visualization of the heart and blood vessels after the injection of contrast media. The present paper is presented to show the development of our use of retrograde arteriography in the visualization of lesions of the aorta and of peripheral vessels.

Sicard and Forestier<sup>1</sup> were the first to visualize the blood vessels of the human extremity through injection of radio-opaque material. Their work in France was followed in the same year by that of Berberich and Hirsch<sup>2</sup> in Germany and by Brooks<sup>3</sup> in this country. The contributions of Dos Santos<sup>4</sup> established the usefulness of angiography as a diagnostic method. Injections are usually made into the blood vessel in the direction of the blood flow; toward the heart for visualization of veins and toward the periphery in the arteries. Visualization of the abdominal aorta by direct puncture below the twelfth rib was first described by Dos Santos<sup>4</sup> and has been extensively used by Nelson,<sup>5</sup> Doss,<sup>6</sup> and Wagner.<sup>7</sup> Radiography of the thoracic aorta was accomplished by Blakemore<sup>8</sup> by means of a needle inserted directly into this structure. More recently Hoyos and Del Campo<sup>9</sup> have described a method for the introduction of 30 c.c. of 70 per cent Diodrast directly into the aorta by way of an 18 gauge needle, in order to visualize the thoracic aorta and coronary vessels.

Farinas<sup>10</sup> in his attempts at abdominal aortography discarded the technic originally suggested by Dos Santos of inserting a needle directly into the lower thoracic aorta through the intact skin, in favor of a retrograde method. He first used a catheter passed up through one of the femoral arteries.

Our first retrograde arteriogram was performed in the following patient by means of the catheter technic described by Farinas.

*Case 1.* This patient, a man of 56, was admitted for the first time to the University of California Hospital in November, 1940, with a diagnosis of bleeding duodenal ulcer. He had had abdominal distress related to meals for approximately 10

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years and three days before admission had suddenly vomited a small amount of blood. He passed tarry stools for the next three days. He had been on a bland diet and in 1930 a gastrointestinal series had demonstrated the crater of an old ulcer. At the time of his admission in 1940 roentgen-ray examination showed an ulcer on the lesser curvature as well as a deformity of the duodenum, suggesting a second ulcer. He recovered uneventfully and was discharged on a bland diet without medication. He was well for two years until in 1942 he noted a tarry stool. Upon readmission his blood pressure was found to be 170 mm. Hg systolic and 115 mm. diastolic. Roentgen-ray examination revealed an ulcer on the bulb of the duodenum and also a small esophageal diverticulum with a questionable ulcer on the lesser curvature of the stomach. At exploratory laparotomy in March of 1942 a mass was discovered behind the stomach just above the pancreas, anterior and attached to the aorta. This mass was spherical, about 7 centimeters in diameter, quite firm and rubbery with an expansile pulsation. Aspiration failed to yield any fluid. A biopsy was performed,  $\frac{1}{4}$  inch of the superficial portion of the lesion being removed. Microscopic examination revealed connective tissue compatible with the diagnosis of an aneurysm. Nothing further was done at the time of this operation. In August of 1942 he was again readmitted because of recurrent melena. There were no further difficulties until November, 1945. At that time he had a sudden onset of nausea, vomiting, and abdominal pain together with melena. The abdominal pain was similar to the episodes of "ulcer discomfort" but much more severe. At this time examination revealed persistent abdominal tenderness and a considerable increase in the size of the upper abdominal tumor. In the succeeding year the abdominal mass became increasingly larger and the patient suffered repeated bouts of severe vomiting and abdominal pain. The possibility of a hemangioma of the liver was considered but the general impression was that he had an aneurysm of the abdominal aorta. He was readmitted to the hospital on September 27, 1946, for visualization of the abdominal aorta.

On October 2, 1946, an attempt was made to pass a catheter into the thoracic aorta by way of the left brachial artery. Through a transverse incision the brachial artery was exposed just below the profunda, and a No. 10 ureteral catheter was passed up this artery under fluoroscopic control. However, at the first portion of the subclavian artery, despite repeated manipulations, the catheter went up into the cervical region rather than down the subclavian into the aorta. Accordingly, the catheter was brought out to the second portion of this artery and 12 c.c. of 70 per cent Diodrast were injected as rapidly as possible. Films taken of the lower abdominal aorta failed to show any dye. The patient suffered a rather alarming reaction associated with tachycardia and a drop in blood pressure, suggesting that the dye had gone into the cerebral circulation possibly by way of the vertebral artery. The catheter was withdrawn and the opening in the brachial artery sutured but thrombosis occurred. Good collateral circulation was present so that no ischemia of the hand developed although the radial pulse on the left side was only barely perceptible.

Because of persisting pain and the increasing size of the abdominal mass the patient was willing to have anything done which might give him relief. On October 15 a second attempt was made to visualize the abdominal aorta. Under local anesthesia, the right femoral artery was exposed just below the profunda. The artery was occluded with two artery clamps and a small transverse incision was made through which a short metal cannula was introduced. Through this cannula a No. 9 ureteral catheter was passed up into the femoral artery. Under fluoroscopic control the catheter could readily be passed up to the aortic arch. It was then withdrawn to a point just above the diaphragm. Twenty c.c. of 70 per cent Diodrast were injected within a period of three to four seconds and roentgen-ray films were taken

in rapid succession. Following withdrawal of the catheter the transverse incision in the superficial femoral artery was sutured but, upon release of the occluding arterial clamps, it was found that thrombosis had taken place above the operative site. Accordingly the common femoral artery was opened just above the profunda and a small thrombus was removed. The artery was irrigated with saline and heparin and the wound was sutured. Following release of the occluding arterial clamps, normal pulsation took place across the suture line and, at the conclusion of the operation, the ankle pulses were normal.

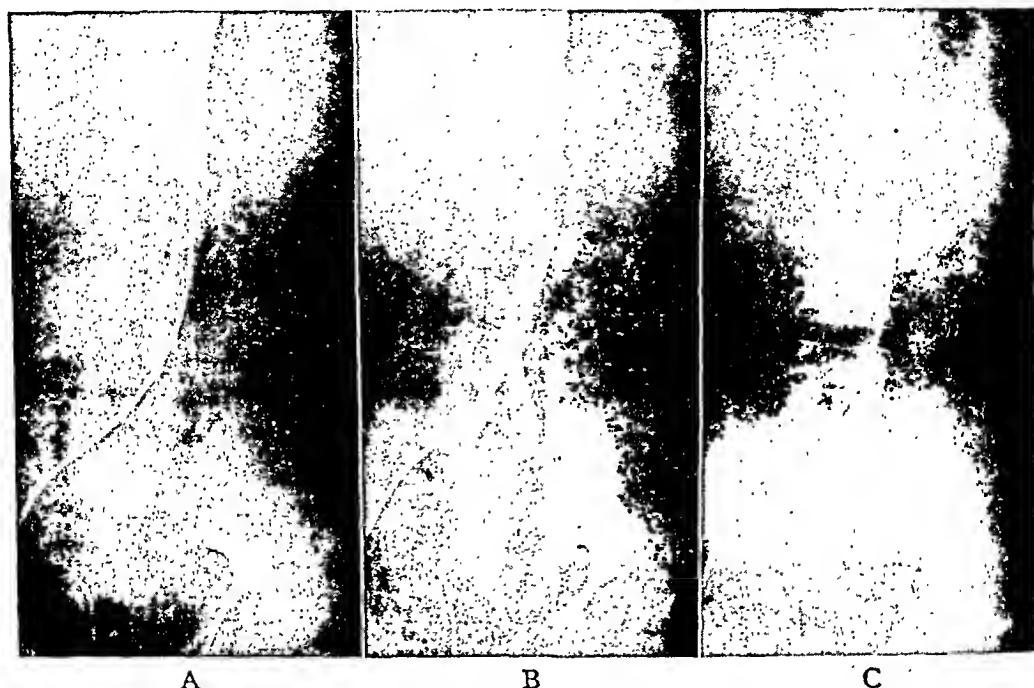


FIG. 1. Arteriogram of abdominal aorta obtained by injection of 70 per cent Diodrast through ureteral catheter inserted by way of right femoral artery.

As shown in figure 1 the upper abdominal aorta was well visualized in the first film and by the time the third film was taken both iliac vessels were well delineated. There was no filling of the mass with radio-opaque material and the aorta did not appear to be dilated and showed a smooth contour. It was accordingly decided that the abdominal aorta was probably not intrinsically diseased and that an attempt could be made to obliterate the aneurysm. Operation was performed on October 25. Through a transverse incision, the abdominal aorta was exposed from the bifurcation to the diaphragm by the retroperitoneal approach previously described.<sup>11</sup> With the aorta occluded above and below the mass, the peritoneum was opened. The aneurysmal sac was widely opened. Old laminated clot was removed and at the bottom two small openings were found which were closed with interrupted stitches of No. 40 cotton. The aneurysmal wall was not removed. The patient recovered and at the present time, 18 months since operation, is completely restored to health.

*Comment:* Retrograde arteriogram of the abdominal aorta in this patient disclosed a normal abdominal aorta and permitted restorative endoaneurysmorrhaphy.

Because of the complications which originated from retrograde arterio-

graphy with the catheter technic we decided to employ the retrograde injection method which Farinas had described in his second contribution.<sup>12</sup> According to this technic 70 per cent Diodrast is injected at 15 pounds pressure through a trocar 1.5 mm. in diameter. The injection is accomplished in two seconds. The next two patients in whom this retrograde technic was applied were patients with coarctation of the aorta but these cases will be reported elsewhere.

The patient is placed supine on a horizontal cassette tunnel; the long axis of the tunnel and the long axis of the roentgen-ray table on which it is placed run in the same direction. The tunnel is open on both of its longer sides and large enough to permit the easy passage of a 14 by 17 inch film cassette through it. A stationary grid is fastened to the top of the tunnel. A preliminary film is taken to check the position of the patient and technic, using a target film distance of 40 inches, 400 milliamperes, one-tenth to one-fifth of a second, and a voltage adjustment to give an exposure which adequately shows the thoracic spine detail.

After the preliminary film has been seen by the radiologist and any necessary corrections in technic made, the needle is inserted into the artery. The distal part of the artery is held shut and the injection is made as rapidly as possible. Seventy per cent Diodrast is the medium used. The dose is on the order of 1 c.c. per kilogram up to a maximum of 50 c.c.

It is imperative that the first film of the series be taken immediately on completion of the injection and the remaining two to three films as rapidly as the cassettes can be changed by hand (about every two seconds).

Retrograde arteriography of the abdominal aorta by retrograde injection of the contrast medium into the femoral artery has not been successful in our hands in four patients. In two of these patients a large abdominal aneurysm was present. In spite of the use of a 15 and a 16 gauge needle, with the injection of 30 to 40 c.c. of 35 per cent or 70 per cent Diodrast, adequate visualization of the abdominal aorta was not obtained. Similarly in two patients with the clinical diagnosis of thrombosed abdominal aorta visualization was not obtained.

Vascular lesions of the upper extremity have been more successfully shown. In the second case which we studied, the right subclavian artery was visualized by retrograde injection of the right common carotid artery.

*Case 2.* This patient was a 41 year old man who was admitted to the University of California Hospital in January, 1947, because of impaired circulation to the right hand of five months' duration. For two months prior to entry he had had severe attacks of Raynaud's phenomenon brought on by exposure to cold and associated with considerable pain. Roentgenograms taken a month before admission disclosed a cervical rib. At the time of admission physical examination revealed a mass above the right clavicle measuring 2 by 3 centimeters, absent pulses in the right upper extremity and atrophy of the muscles of the hand, forearm, and arm. There was no pulsation or bruit heard over the mass. The tip of the right index finger and thumb showed small areas of necrosis.

On January 25, under local anesthesia, the right common carotid artery was exposed and 20 c.c. of Thorotrast were injected in retrograde fashion. The first roentgen-ray film (figure 2) showed filling of the common carotid, innominate, and first portion of the subclavian artery with obstruction of the artery just beyond the thyro-

cervical axis. The collateral circulation was well visualized. The second film showed an irregular filling defect of the brachial artery at the profunda which suggested that there had been an embolic occlusion of this vessel. The patient was operated upon on January 30 and a thrombosed aneurysm of the third portion of the subclavian artery was discovered. The scalenus muscle was divided and a section of the aneurysm was removed. Following this operation there was abrupt relief of pain and a cessation of the attacks of Raynaud's phenomenon. Thirteen months after operation his hand was warm, there was no ulceration, and he was able to do full-time work. Oscillometry revealed a return of pulsation in the right forearm.

*Comment:* Retrograde arteriography was useful in this patient in visualizing the first and second portions of the right subclavian artery. This artery would have been difficult to inject by direct puncture. Visualization of the collateral circulation was of assistance at the time of operation.

Occasionally the location of the lesion may be such as to make it difficult to inject the contrast medium into the artery proximally. The following two examples are cited.



FIG. 2. A.



FIG. 2. B.

FIG. 2. Thrombosed subclavian aneurysm distal to cervical rib. Arteriogram obtained by injecting Thorotrast in a retrograde fashion into the right common carotid artery.

*Case 4.* This patient was a 12 year old boy who was admitted to the University of California Hospital on May 10, 1947, because of a large angioma involving the entire right arm, hand, and shoulder. The discoloration had been noted since birth and the patient had experienced recurrent attacks of pain, possibly associated with thrombophlebitis involving the venous component of the angioma. There was no osteohypertrophy but there was considerable soft tissue enlargement. Although there was no bruit audible over the right upper extremity the skin was warmer than on the normal side and it was felt that there might be some arterial component to the angioma. Accordingly, on May 9, 1947, a retrograde injection of the arteries of the right upper extremity was performed through the right radial artery. Under general anesthesia the right radial artery was occluded at the wrist and 30 c.c. of 35 per cent Diodrast were injected in retrograde fashion through a 16 gauge needle. Serial roentgen-ray films were taken. The needle was then removed and an attempt made to suture the artery but because of the trauma from the needle puncture thrombosis took place. However, there was no impairment of circulation to the hand. The films (figure 3) showed a normal arterial supply to the right upper extremity but

tremendous enlargement of the superficial veins. On May 22, 1947, the venous angioma of the palm of the right hand and little finger was resected. Necrosis of the distal half of the little finger followed this operation but removal of this portion of the angioma resulted in a great decrease in the size of the veins on the dorsum of the hand and forearm.



FIG. 3. Angiograms of the right upper extremity obtained by injecting 35 per cent Diodrast into the radial artery. The first film shows the filling of the arterial tree. The second film shows the filling of the greatly dilated veins.

*Comment:* Retrograde arteriography in this patient was useful in showing that there was no significant arterial component to the angioma. Although possible, injection of the main artery proximal to the lesion would have been difficult.

*Case 11.* This patient was a 34 year old female who was admitted to the University of California Hospital on February 11, 1948, because of a large swelling over the left scapula which had been present for three years. Operation previously performed at another hospital had revealed an angioma but the bleeding had been so severe that only a small portion of the lesion was excised for histological examination.

On physical examination there was marked pulsation of the axillary artery with a continuous thrill and bruit over the vessels high in the axilla. The mass over the dorsum of the scapula was pulsatile but quite firm and rubbery. The circumflex scapular vessels and the long thoracic artery were dilated. Upon occlusion of the subclavian artery the pulse rate dropped from 88 to 76 beats per minute. There was no enlargement of the heart nor decreased exercise tolerance.



FIG. 4. Arteriogram of a congenital arteriovenous fistula of the left axillary and scapular vessels obtained by injecting 70 per cent Diodrast in a retrograde fashion into the brachial artery.

Retrograde arteriography was performed on February 14. The brachial artery was exposed below the profunda and by means of a 16 gauge needle 30 c.c. of 70 per cent Diodrast were rapidly injected. Serial roentgen-ray films were taken. As shown in figure 4 there was a large communication between the brachial artery and the angiomatous mass which filled the left axilla. The second film showed that the Diodrast passed into the venous side of the circulation so that an angiocardigram was obtained. At operation on February 20, 1948, the left axillary artery was surrounded by a segment of rubber tubing and all the branches were divided and ligated from the clavicle down to the fistulous communication which was found to be just distal to the subscapular artery. This communication was closed with a transverse suture and the continuity of the artery restored. Following closure of the arterial component of the angioma the subscapularis and infraspinatus muscles were excised with the axillary contents. Except for temporary edema of the left arm the patient recovered completely from this operation, and there has been no recurrence of the bruit. Histological section revealed an angioma which was invading the muscles but which was composed of mature cells.

*Comment:* Retrograde arteriography in this patient was useful in visualizing an arteriovenous fistula located high in the left axilla. The brachial artery was severely traumatized by insertion of the 16 gauge needle so that several stitches of No. 00000 Deknatel were necessary to control bleeding following release of the artery clamps. It is believed that thrombosis probably took place at the suture line since the pulse on the left side was diminished in volume immediately following the arteriogram. However, there was no impairment of the circulation to the left hand. In retrospect, it would have been quite as satisfactory to have performed the arteriogram by direct injection of the contrast medium into either the subclavian or the axillary arteries.

Visualization of aneurysms of the thoracic aorta and innominate artery was attempted on three occasions but the results were not entirely satisfactory, presumably because of the difficulty of introducing a sufficient quantity of radio-opaque material rapidly. In one patient a complication resulted.

*Case 6.* This patient had been admitted to the University of California Hospital on numerous occasions since August, 1945, because of swelling of the left arm and neck with a bruit audible in the left ear. He was 70 years old at the time he was first admitted and had noted rather rapid onset of swelling of the left arm, forearm, and hand five weeks before entry. Angiocardigrams with intravenous injection of 50 c.c. of 70 per cent Diodrast through a 16 gauge needle into the left antecubital vein showed simply venous obstruction in the mediastinum with filling of collateral veins. On September 3, 1945, 20 c.c. of 70 per cent Diodrast were injected both into a vein of the right arm and into a vein of the left arm and these injections revealed a mediastinal mass which brought about a high degree of obstruction of the subclavian vein on the left although the right side was not completely blocked. Filling of the mass was not observed. Retrograde brachial arteriogram on June 3, 1947, with 50 c.c. of 35 per cent Diodrast failed to outline the aorta. However, when 50 c.c. of 70 per cent Diodrast were injected in the same fashion the aorta was outlined. An aneurysm involving the descending portion together with a large mass filling the anterior





FIG. 5. Aneurysm of aortic arch. *A*. Phlebogram of left arm showing obstruction of the innominate vein. *B*. Arteriogram obtained by injecting 70 per cent Diodrast in a retrograde fashion into the right brachial artery.

superior mediastinum was made out (figure 5). The tortuous innominate artery could be seen.

Immediately after the injection of the contrast medium the patient had a convulsion, and for a period of several hours was in a state of markedly depressed circulation. This complication probably is attributable to the fact that no attempt was made to block the passage of Diodrast into the right carotid artery. Spontaneous recovery took place but his condition was thought to be inoperable.

*Comment:* Retrograde arteriography in this patient was moderately successful in visualizing a vascular mass filling the superior mediastinum.

The results in all the patients in whom an attempt has been made to visualize the aorta or peripheral arteries by retrograde arteriography are shown in table 1. Retrograde arteriography was done by direct puncture of the exposed artery, with injection of the contrast medium through a 15. or 16 gauge needle. Thrombosis of the artery occurred in three patients, although distal ischemia was not produced. Convulsions occurred in two patients with the use of 70 per cent Diodrast. In both of these cases the Diodrast was not prevented from entering the cerebral circulation.

TABLE I

Case No.	Sex	Age	Date	Clinical Diagnosis	Artery	Size Needle	Contrast Medium	Anes- thetic	Com- plica- tions	Comments
1	M	60	10/15/46	Abdominal aneurysm	Rt. femoral	No. 9 cath- eter	20 c.c. 70% Diodrast	Local	Throm- bosed femoral	Normal aorta confirmed at operation
2	M	41	1/27/47	Subclavian aneurysm	Rt. carotid		20 c.c. Thoro- trast	Local	0	Thrombosed aneurysm con- firmed at op.
3	M	46	2/28/47	Left iliac thrombosis	Lt. femoral		20 c.c. Thoro- trast	Local	0	Unsuccessful
4	M	12	5/ 9/47	Angioma right arm	Rt. radial	16	30 c.c. 35% Diodrast	Ether	Throm- bosed artery	Venous an- gioma
5	F	55	5/18/47	Aneurysm ab- dominal aorta	Lt. femoral	16	40 c.c. 35% Diodrast	Gas Oxygen	0	Unsuccessful
6	M	72	6/ 2/47	Aneurysm thoracic aorta	Rt. brachial	16	50 c.c. 35% Diodrast 50 c.c. 70% Diodrast	Local	Con- vulsion	Aneurysm arch aorta
7	F	30	6/25/47	Aneurysm ab- dominal aorta	Rt. femoral	15	30 c.c. 70% Diodrast	Local	0	Unsuccessful
8	M		12/13/47	Retrosopha- geal right subclavian	Rt. brachial			Local	0	? Aneurysm thoracic aorta
9	F	52	1/ 7/48	Obliterated ab- dominal aorta	Rt. femoral	16	20 c.c. 20% Thorotrast	Aver- tln— local	0	Unsuccessful
10	F		2/ 3/48	Aneurysm right carotid	Rt. brachial			Local	0	Unsuccessful
11	F	34	2/14/48	Arteriovenous fistula with angioma axilla.	Lt. brachial	16	30 c.c. 70% Diodrast	Local	Throm- bosed artery	Fistula and angioma con- firmed at operation.

## DISCUSSION

Although arteriography can best be accomplished by the injection of radio-opaque material into the artery proximal to the lesion to be studied, occasionally the location of the lesion or its character makes it difficult to carry out this technic. Under such circumstances, retrograde arteriography may offer a method for adequate visualization. We have not been successful in our attempts at visualization of the abdominal aorta except in the patient in whom the catheter was introduced through a cannula inserted into the femoral artery (figure 1). In animal experiments Farinas showed fluoroscopically that to be successful the injection must first overcome the inertia of the blood flow and, second, must overcome the blood pressure. It may be that injection of a larger quantity of solution under higher pressure would have yielded more satisfactory results. The danger of thrombosis at the site of injection, especially where a large needle is inserted into a small artery, is very real. This thrombosis occurred in three of the patients shown in table 1. With the use of 70 per cent Diodrast, the possibility of serious systemic reaction should be considered, especially when there is any opportunity for the contrast medium to enter the cerebral circulation. Although iodine compounds are known to induce spasm,<sup>12</sup> we have not hesitated to use this material in the peripheral arterial lesions, provided there was no impairment of circulation.

## CONCLUSIONS

1. Retrograde arteriography has been used in 11 patients for visualization of vascular lesions involving the peripheral arteries, and the abdominal and thoracic aorta.
2. Retrograde arteriography can be used in those patients in whom it is difficult or impossible to introduce the radio-opaque substance into the artery proximal to the lesion.
3. Attention is called to the complications which may result from the use of this method.

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# THE TREATMENT OF ACUTE PUTRID LUNG ABSCESS WITH PENICILLIN AND SULFADIAZINE \*

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ACUTE putrid lung abscess is one of the most serious of intrathoracic diseases. On the one hand it may lead to an early fatal termination because of toxemia, hemoptysis, embolic phenomena, spill over to the contralateral lung and rupture into the pleura. On the other hand, if an early fatal issue does not ensue, the acute becomes a chronic lung abscess which rarely resolves and requires extensive and difficult surgical intervention and, at best, a prolonged and costly convalescence if recovery or improvement is to be hoped for.

Spontaneous recovery from acute putrid lung abscess occurs in but a small percentage of cases. At the Harlem Hospital in the past few years spontaneous recoveries were noted only in 11 per cent of 70 patients with this disease. The favorable outcome occurred in patients with small, uncomplicated abscesses, little toxemia and limited perifocal pneumonitis.

Numerous remedies have been suggested in the treatment of this disease. Indeed many chemicals, autogenous and stock vaccines, postural drainage, bacteriophages, and even pneumothorax have come in for therapeutic praise by various observers. But the fact that the reported successes have not been reproduced with the respective methods of care in any large group of such patients prompts the suggestion that the cures reported might have occurred spontaneously.

With the advance in our knowledge of the pathogenesis and pathologic physiology of putrid lung abscess and the recognition of the ineffectiveness of treatment by medical means, it was inevitable that surgical intervention should be resorted to in their management.

At first it was felt that large abscesses, or those accompanied by great toxicity and slow roentgenologic improvement, were best treated by early thoracotomy and pneumonostomy. This was also true of abscesses which progressed and ruptured into the pleura, or gave rise to persistent hemoptysis.

In recent years, however, there has been a growing tendency to have all acute lung abscesses, regardless of their size or the severity of their toxic manifestations, treated surgically as soon as the diagnosis is made. This view received encouragement from the reports of many chest surgeons, notably Neuhof and Touroff,<sup>1</sup> who in 1940 reported 73 recoveries in 86 patients operated on for the relief of this condition. Sweet, on the other

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hand, in the same year reported only 43 per cent cured of 125 patients treated surgically at the Massachusetts General Hospital. Sweet<sup>2</sup> was of the opinion that the results of surgical treatment of lung abscess were on the whole disappointing. He stated that if there is a good chance of spontaneous recovery, operation should be avoided. A similar view was expressed by Cutler<sup>3</sup> in 1936.

There are, however, no reliable criteria by which we can determine just when an acute lung abscess has reached a point when spontaneous recovery is no longer to be expected. On the other hand, waiting too long for such a recovery often results in the acute becoming a chronic abscess. In the first instance, because the lesion resolves slowly, we may expose the patient to a needless and often dangerous major operation, while if we procrastinate the resulting chronic abscess will require extensive surgical interference, attended by high mortality and morbidity and at best a prolonged, stormy and costly convalescence.

A consideration of these facts makes it quite obvious that we are in need of a treatment which would (1) increase the rate of recovery within the shortest possible period of time without surgical interference; (2) decrease the number and severity of pre- and post-operative complications in those who will have to be treated surgically.

When penicillin became freely available, we decided to study its potentialities in the treatment of putrid lung abscess and administered it to six patients with acute, and seven with the chronic form of this disease in 1944 and 1945. Sulfadiazine was employed concurrently, despite the fact that when used by itself it had given no relief in a small series of cases so treated. But its synergistic action with the antibiotic was becoming recognized, and it was hoped that it might have a beneficial effect on the ever present perifocal pneumonitis. The excellent results obtained and reported elsewhere<sup>4</sup> encouraged us to continue this method of treatment in 15 additional cases of acute putrid lung abscess in the past 15 months, and the 21 cases form the basis of this presentation.

As soon as a diagnosis of putrid lung abscess was definitely established and confirmed by chest roentgenograms, the patient was given both penicillin and sulfadiazine. The sodium salt of penicillin was administered intramuscularly in doses of 40,000 units every three hours. The sulfadiazine was given in the usual manner, sufficient to establish and maintain adequate blood levels. Occasionally much larger doses of penicillin were deemed desirable, and in a few cases we changed the brand of the antibiotic to obtain the desired results. But in no instance did we change the route or frequency of its administration. Moreover, the treatment was continued until all clinical and roentgenologic evidence of pulmonary involvement had disappeared.

## CASE REPORTS

*Case 7.* A man, 41 years old, entered the Harlem Hospital on December 12, 1945. In the past six months he had coughed on and off and had lost 16 pounds in weight. On the day of admission he had noted pain in the left chest, his temperature was 104° F. and his sputum was fetid. The initial chest roentgenogram revealed a moderate sized cavity with extensive pneumonic involvement in the left upper lobe. There were also small infiltrations in the right upper lobe. He was immediately placed on sulfadiazine and 25,000 units of penicillin every three hours. The infiltrations and the cavity began to regress and his temperature became normal on December 16, 1945. By January 9, 1946 the chest film revealed only a slight thickening of the pleura over the left upper lobe. The chest film of February 9, 1946 revealed no gross abnormality, and he was discharged as cured on February 11, 1946.

*Comment:* Uneventful recovery from a putrid lung abscess and some contralateral pneumonia with sulfadiazine and penicillin therapy.



FIG. 1. *Case 7.* Film taken December 14, 1945 shows extensive cavitation with a wide fluid level in the left upper lobe.



FIG. 2. *Case 7.* Taken February 9, 1946. Shows both lungs clear.

*Case 8.* A man 26 years old, entered the pneumonia service of Harlem Hospital on December 30, 1945 complaining of shortness of breath and a sore throat which was accompanied by fever, cough and a pain in the chest. His temperature was 103° F. and he was extremely toxic and jaundiced. A type 3 pneumococcus was recovered from the sputum. The chest film of January 2 revealed consolidation of the entire right upper lobe with patchy consolidation of both bases. He was treated with sulfadiazine until January 12, 1946 without any benefit. On January 12 the sputum became profuse and foul and a large cavity was noted in the right axilla. He was given 50,000 units of penicillin every three hours and by January 16 the temperature was normal. The chest film of January 25, 1946 revealed no abnormality except for two small emphysematous blebs in the right upper lobe. On February 15 the chest film was normal and he was discharged cured on March 1, 1946.

*Comment:* The patient had an extremely toxic acute putrid lung abscess with putrid pneumonia in both lower lobes. The administration of sulfadiazine failed to produce any improvement. The addition of penicillin in adequate dosage was followed by rapid and complete recovery.



*Case 9.* A man 54 years of age, was admitted to Harlem Hospital on January 6, 1946. He was a chronic alcoholic and had a history of cirrhosis of the liver. Three weeks before admission he noted a productive cough with dark sputum. A week later he had severe pain in his right chest. His temperature on admission was 104° F. He coughed severely and had foul sputum. His liver was enlarged to three and one-half fingers below the right costal margin. The initial chest film revealed a large cavity with a fluid level occupying one-third of the right upper lobe. There was also a pneumonic involvement of the right lower lobe. The heart was enlarged in the region of the left ventricle. He was given sulfadiazine on January 7, 1946, but his temperature rose to 105° F. On January 10 he received in addition 30,000 units of penicillin every three hours and this was continued until March 18, 1946. The chest film of January 18, 1946 revealed fluid filling the entire cavity, indicating a block of the draining bronchus. Despite this, the temperature had become normal on January 16, 1946 and remained normal until his discharge. The chest roentgenogram of January 24, 1946 again revealed a large cavity. Serial roentgenograms thereafter showed progressive clearing of the lung and the final film taken March 15, 1946 revealed a few fibrotic nodules in the right upper lobe. He was entirely free of symptoms and was discharged completely cured on April 15, 1946.

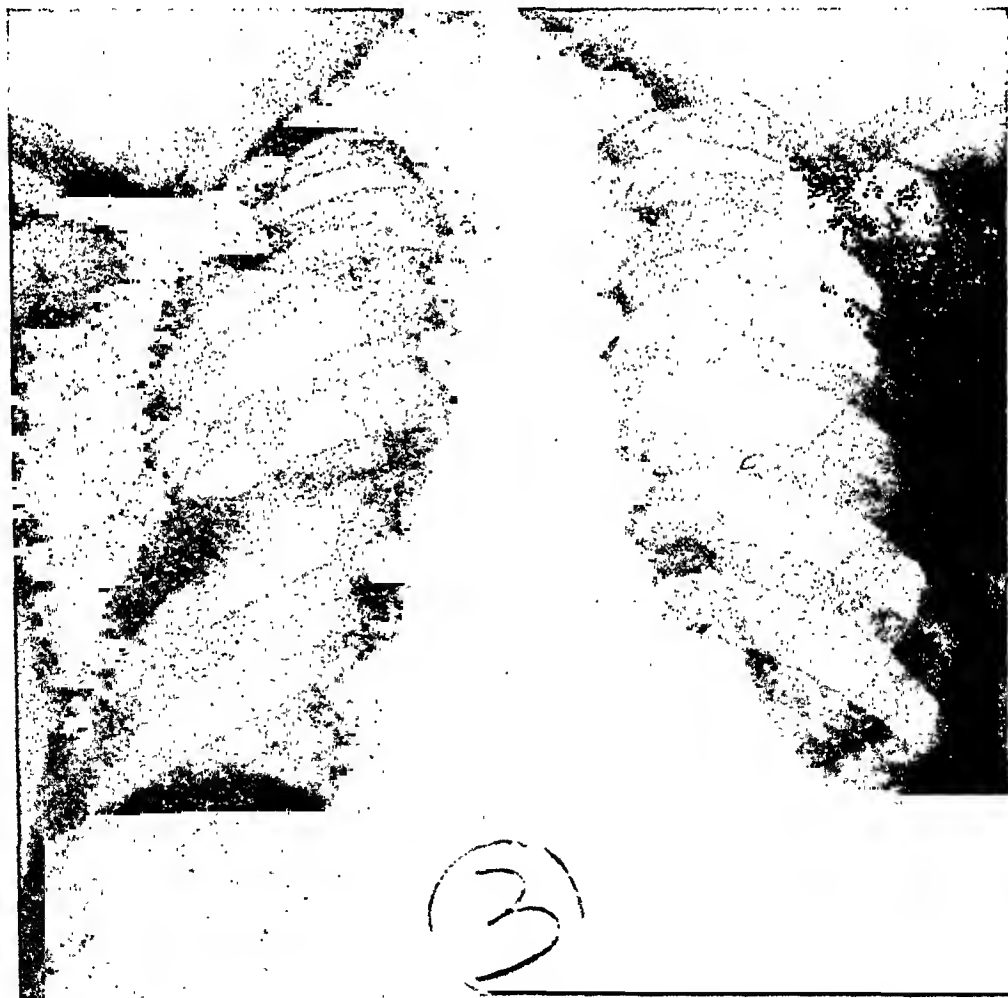


FIG. 3. *Case 8.* Film taken January 12, 1946 shows large abscess with fluid level in the right upper lobe.

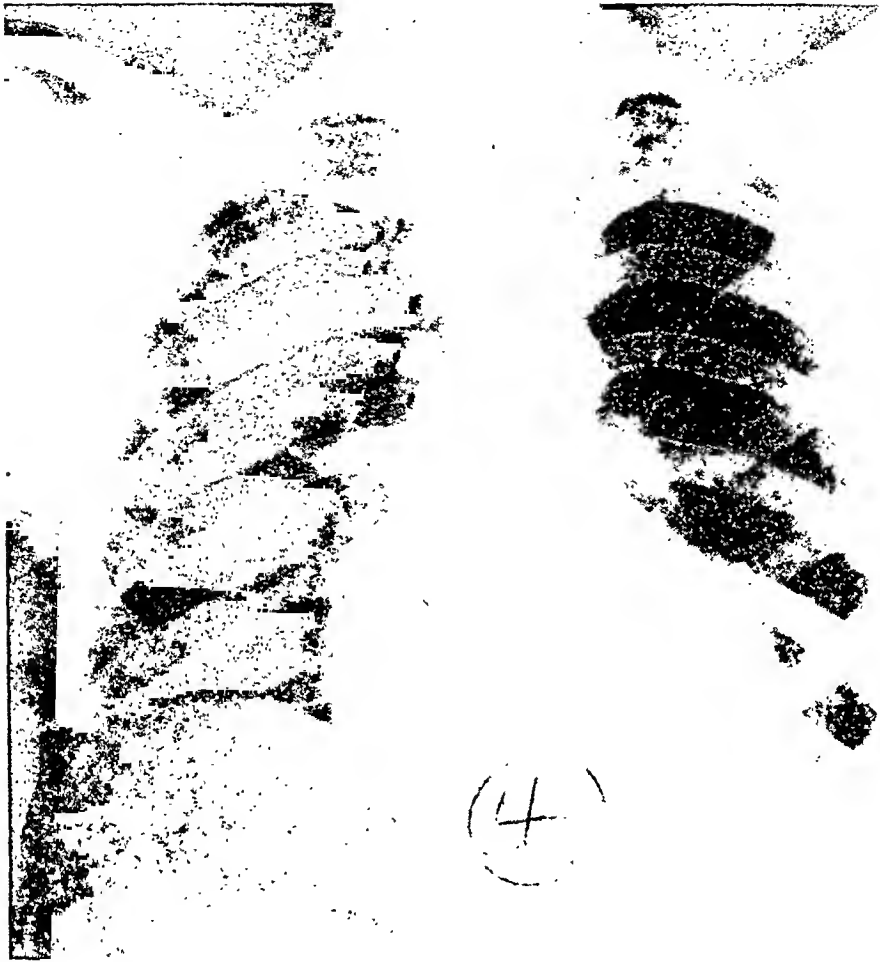


FIG. 4. Case 8. Taken February 15, 1946. Shows clear lungs.

*Comment:* Complete recovery from a large acute putrid lung abscess with a blocked cavity under treatment with sulfadiazine and penicillin. This patient was in poor condition and had cirrhosis of the liver.

*Case 10.* A 32 year old Negro, a chronic alcoholic, entered the Harlem Hospital with foul sputum and a temperature of 102° F. on February 18, 1946. He stated that he had been sick for two weeks with a productive cough and fever. The chest roentgenogram revealed a large cavity with extensive pneumonic involvement in the upper lobe of the left lung. He was immediately placed on sulfadiazine and 25,000 units of penicillin every three hours. His temperature became normal on February 26, 1946, and continued normal until discharge. Serial chest roentgenograms showed progressive regression of the pneumonic area. The fluid level in the cavity disappeared on March 19, 1946, and the cavity was no longer visible a week later. When he was discharged on May 7, 1946, the chest film revealed a few fibrotic strands in the left upper lobe.

*Comment:* Uneventful recovery from a large acute putrid lung abscess with slight residual fibrotic change.

*Case 11.* A 32 year old Negro entered the Harlem Hospital on June 10, 1946, complaining of cough, weakness, expectoration of greenish sputum following exposure to wet weather a week before. On admission his temperature was 102° F. His sputum was foul and copious. There were moist râles and dullness throughout the right lower lobe. The initial chest film revealed a large abscess with fluid level surrounded by large nodular pneumonic infiltration scattered throughout the entire right lower lobe. He was given sulfadiazine and 30,000 units of penicillin every three hours. Despite this, the temperature rose to 104° F. By June 17, the serial chest films revealed a marked spread of the disease to the left lung. The penicillin was raised to 50,000 units every three hours. Nevertheless he became extremely cyanotic and dyspneic and there was a further spread throughout both lungs. He was extremely toxic and gravely ill, and the surgical consultant felt he would not survive operative interference. He was given oxygen, intravenous feedings and transfusions



FIG. 5. Case 9. Taken January 8, 1946. Shows very large abscess occupying major portion of right upper lobe.

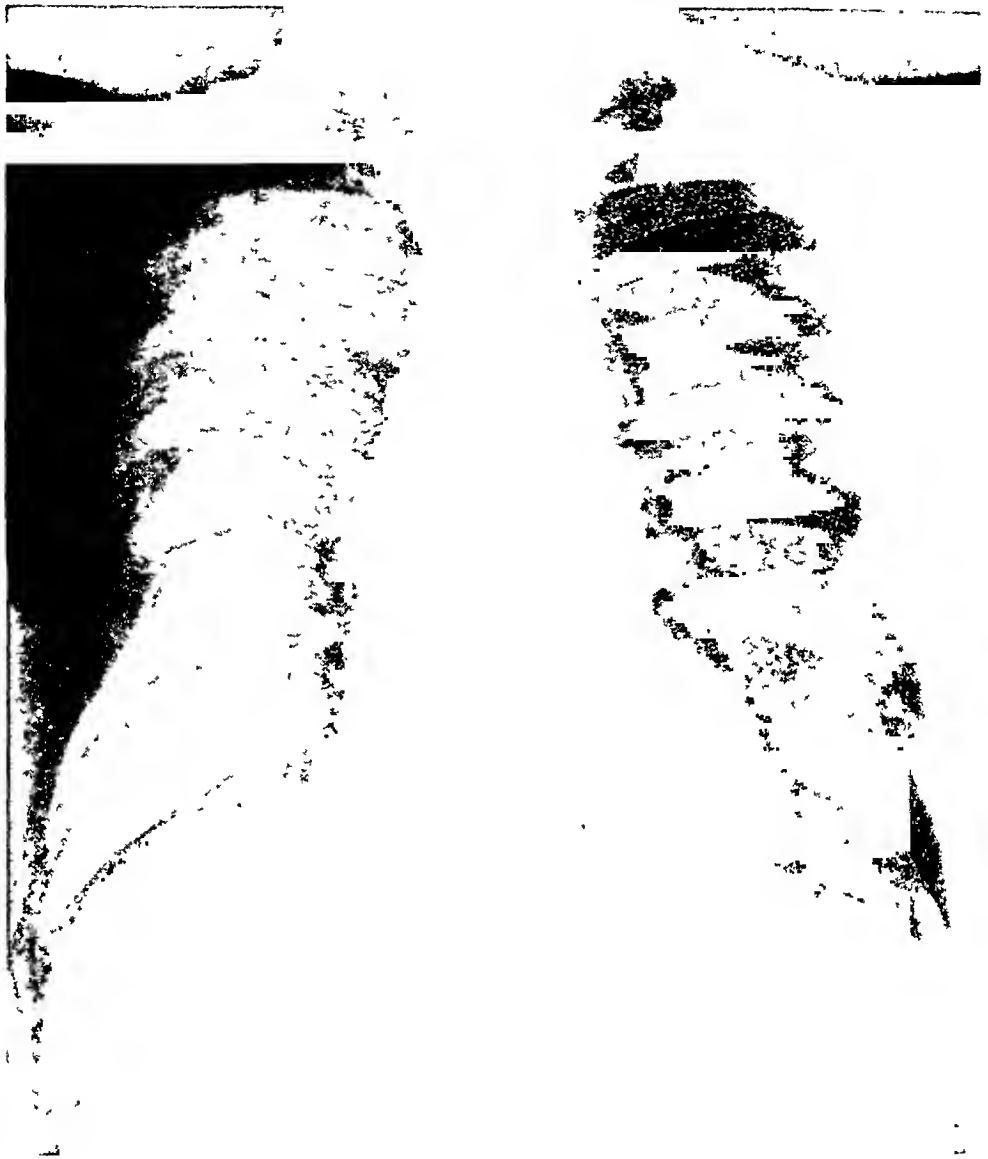


FIG. 6. Case 9. Taken March 26, 1946. Shows no evidence of abscess.

and the penicillin was raised to 100,000 units every three hours on June 27, 1946. The following day the temperature began to fall and the chest film of July 1 showed some slight improvement. By July 15 the temperature had returned to normal. He was no longer toxic and the infiltrations in the left lung had disappeared. On August 6, 1946 the cavity in the right lung was no longer visible. On August 13 the chest film failed to reveal any abnormality except for slight fibrosis in the medial aspect of the right lower lobe. The penicillin was discontinued on August 15, and he was discharged cured on September 4, 1946.

*Comment:* The patient was extremely toxic and sustained an early spill-over to all lobes on both sides. It was thought that he would not survive surgical care. We were not able to study the resistance of the infecting organisms to the penicillin used, but there can be no doubt that the patient's

life was saved by the increase in the dose of the antibiotic and persistence of its administration.

*Case 12.* An epileptic, 27 years of age, entered the Harlem Hospital on June 16, 1946. She had been ill for 10 days with chills, fever and a productive cough. Her temperature was 104° F. on admission, and the initial chest film on June 20 revealed a cavity in the right upper lobe. Foul sputum was noted on June 22. She had been given sulfadiazine and 25,000 units of penicillin intramuscularly every three hours since her admission without benefit. The penicillin dosage was therefore raised to 40,000 units on June 21. No improvement was noted by June 25 and surgery was contemplated. However, on June 27 the temperature became normal. By July 8 the lung had cleared markedly and the film of July 15 no longer revealed cavitation.

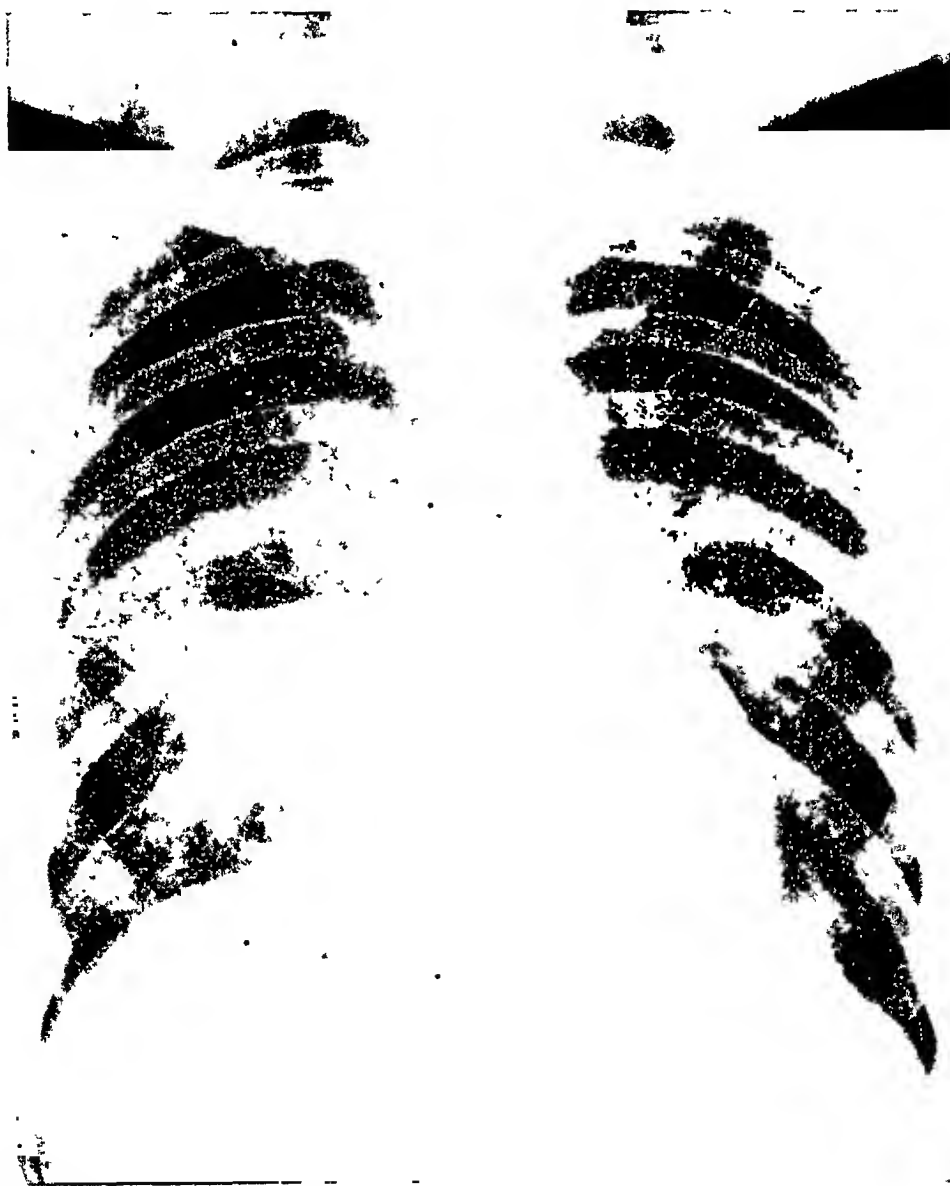


FIG. 7. *Case 11.* Film taken June 11, 1946 shows large abscess in the right upper lobe.



FIG. 8. *Case 11* Taken July 7, 1946. Shows marked spillover to the opposite side

On July 23, while the right side was clearing, a small pneumonic infiltration was noted in the left lower lobe, and the penicillin was raised to 50,000 units per dose. Improvement ensued and the chest film of July 27 revealed no abnormality. Bronchography on August 7 was normal. Penicillin was discontinued on August 25, 1946. She was discharged as cured of her lung abscess on September 14, 1946

*Comment:* This case again illustrates the need of increasing the dosage of penicillin when clearing of the lesion is retarded, or when a spillover ensues.

*Case 15.* A 36 year old man was admitted to Harlem Hospital on August 14, 1946 with a history of seven days' illness, cough, expectoration and fever. His temperature was 103° F., and he had copious foul expectoration. The initial chest film showed consolidation of the entire right upper lobe with a high-light suggesting early cavitation. Sulfadiazine was started on the day of admission, but there was no effect

upon the temperature. On August 18 he was given in addition 50,000 units of penicillin intramuscularly every three hours. The temperature fell by lysis and was normal after August 22, 1946. However, the chest film of August 27, 1946 revealed a large cavity, although there was much less pneumonitis. Penicillin was continued and the chest roentgenogram of September 11 no longer revealed cavitation. The final roentgenogram of October 1, 1946 showed no abnormal shadows. He was discharged cured on October 3, 1946.

*Comment:* Complete and rapid recovery from a large putrid lung abscess under treatment with sulfadiazine and penicillin.

*Case 14.* A 36 year old man entered the Harlem Hospital on September 8, 1946 with a temperature of 104° F. For two weeks he had had chills, fever, weakness and a productive cough. On September 7 his sputum became foul. Initial chest roentgenogram revealed a consolidation of the right upper lobe, and he was given sulfadiazine and 40,000 units of penicillin every three hours. This dose was continued

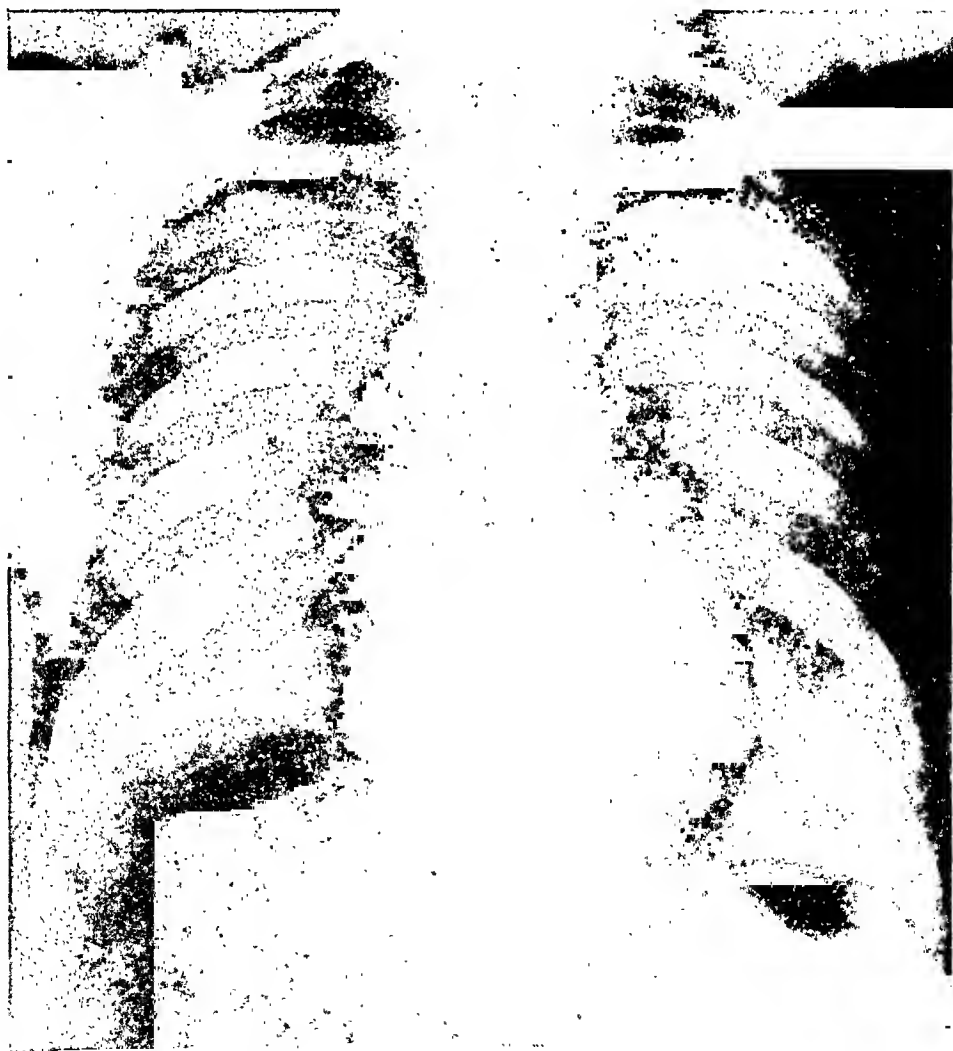


FIG. 9. *Case 11.* Taken August 20, 1946. Shows clear lungs.



FIG. 10. *Case 12.* Taken September 22, 1946. Shows large cavity in the right upper lobe with fluid level.

until his discharge. On September 14, although there was no change in the chest film of that date, the temperature had become normal and the foul odor of his sputum disappeared. The chest film of September 21, 1946 revealed marked clearing with residual pleural thickening and an elevated right diaphragm. The final roentgenogram of October 1, 1946 revealed slight thickening of the pleura. He was discharged on October 3, 1946.

*Comment:* Acute putrid lung abscess which was cured promptly with sulfadiazine and penicillin.

*Case 15.* A 26 year old Negress entered the Harlem Hospital on September 21, 1946 complaining of increasing pain in the right chest of two weeks' duration. She had chills, fever, and bloody sputum, and her temperature on admission was 104° F. The initial chest film revealed a 3 cm. cavity within a pneumonic infiltration in the



upper portion of the right lower lobe. The sputum was copious and foul. She was started immediately on sulfadiazine and penicillin (50,000 units every three hours). Her temperature reached the normal on September 26 and the penicillin dosage was reduced to 30,000 units. On October 4 the cavity had disappeared and the penicillin dose was further reduced to 20,000 units. On October 21, 1946 the chest film was clear, and she was discharged as cured on October 25, 1946.

*Comment:* Uneventful recovery from an acute lung abscess with penicillin and sulfadiazine therapy.

*Case 16.* A 24 year old Negress entered the Harlem Hospital on December 9, 1946. She had had chronic upper respiratory disease for one year. Three weeks prior to admission her cough became much worse and the sputum became blood tinged. Two weeks later she noted foul sputum and fever, and experienced inspiratory pain in the right chest. On admission her temperature was 101° F. Dullness and numerous moist râles were elicited over the right lower lobe posteriorly. The ad-



FIG. 11. Case 12. Taken October 21, 1946. Shows no evidence of abscess.



FIG. 12. *Case 14.* Film taken September 8, 1946 shows abscess formation but no fluid level in the right lower lobe.

mission chest film revealed two cavities with fluid levels and much perifocal pneumonia in the right lower lobe. She was given sulfadiazine on admission and penicillin was started on December 13, 1946, in doses of 50,000 units every three hours. This therapy was continued until her discharge. The sputum ceased to be foul and the temperature became normal on December 15, 1946. The chest film of December 26, 1946 failed to reveal any cavities and by January 15 the roentgenogram was that of a normal lung. Lipiodol bronchography on January 20, 1947 failed to reveal any abnormality of the lower lobes of the lung. She was discharged as cured on January 31, 1947.

*Comment:* Uneventful cure of multiple lung abscesses with penicillin and sulfadiazine.

*Case 17.* An asthmatic 24 year old Negress was admitted to the Surgical Ward of the Harlem Hospital on November 18, 1946, where a subtotal thyroidectomy was done for a non-toxic thyroid adenoma. She was discharged feeling perfectly well, but on December 6, 1946 she began to cough and experienced pain in the right chest. Her cough soon became productive of large amounts of foul sputum. A few days later she noted marked pain in the right shoulder extending down the arm. She was re-admitted to Harlem Hospital on December 15, 1946 with a temperature of 102.8° F.

There were scattered sibilant râles throughout both lungs, as well as numerous large moist râles in the right base and axilla. There was marked tenderness over the right chest in the region of the sixth and seventh dorsal nerves and over the right shoulder joint. She was given sulfadiazine for four days without any effect on the temperature. On December 19 she was given 30,000 units of penicillin every three hours in addition to the sulfadiazine. The initial roentgenogram revealed an area of consolidation of about 4 cm. in diameter in the region of the right costophrenic sinus. (Careful reëxamination of this film on January 22, 1947 showed the presence



FIG. 13. *Case 14.* Taken October 1, 1946. Shows a clearing of the lesion.

of a cavity in the area first thought to be an infarct or pneumonia.) Two days after the penicillin was started the temperature became normal and the cough and expectoration diminished greatly. The penicillin and sulfadiazine were discontinued on January 5, 1947 because of a provisional diagnosis of pulmonary infarct. A paravertebral block of the fifth, sixth and seventh dorsal nerve routes was done on January 17, 1947, with temporary relief of the severe pain in the chest and shoulder. The chest films of January 15 and 20 revealed a gradual increase of the area of consolidation with cavity formation. Sulfadiazine and 100,000 units of penicillin every three hours were again administered and continued until she left the hospital. The chest films of February 24, 1947 and March 10, 1947 showed complete disappearance of the cavity and the area of consolidation almost completely resolved. She left against advice on March 12, 1947.

*Comment:* A case of abscess in the lung following thyroidectomy, in whom the penicillin injections were for a time discontinued because of symptomatic improvement and a temporary diagnosis of pulmonary infarction. Restudy of the early films showed cavitation. The lesion cleared when patient was again placed on sulfadiazine and penicillin in large doses.

*Case 18.* A 36 year old Negress entered the Harlem Hospital on January 5, 1947. She had had a cough for one month, and pain in the left chest and fever for two weeks prior to admission. She expectorated foul and bloody sputum. She felt nauseated, vomited frequently and had nightly sweats.

She had a temperature of 104° F. and was acutely ill. The breath and sputum were extremely foul. Numerous moist râles were heard over the right base posteriorly and at the right axilla. The initial chest film revealed an area of consolidation, as well as a cavity with a fluid level in the right lower lobe. The sputum contained no acid-fast bacilli, and on culture a *Streptococcus hemolyticus* alpha and *Staphylococcus albus* were noted. Sulfadiazine was administered for three days without effect. On January 8 penicillin in 40,000 unit doses every three hours was added, and continued until her discharge. Her temperature became normal on January 10. By January 25, 1947 the cavity could no longer be visualized, and there was a marked decrease in the pneumonic reaction. On February 4 there was further clearing of the pneumonic infiltration. She has had no symptoms or sputum since January 10, 1947. She left against advice on February 10, 1947.

*Comment:* Lung abscess cleared when penicillin was added to the treatment with sulfadiazine.

*Case 19.* A 29 year old Negro entered the Harlem Hospital on February 8, 1947. He had had fever for two weeks, and 10 days before admission had noticed bloody and foul sputum. He complained of a severe pain in his left chest and a loss of 12 pounds in weight.

On admission his temperature was 100° F. and he had profuse and foul expectoration. The initial chest film revealed a rounded infiltration in the mid-zone of the left lung, with a 3 cm. cavity at its center. He was immediately given sulfadiazine and 40,000 units of penicillin every three hours. The sputum was negative for acid-fast bacilli. In three days the cough, expectoration and pain had disappeared. A chest film taken 10 days after admission showed marked clearing of the pneumonic consolidation. On February 24 the chest film showed further clearing. On March 4 a generalized erythematous rash was noticed, and since this was believed to be due to sulfadiazine, its administration was discontinued. The chest film of March 11, 1947 revealed normal lung fields. Penicillin was continued until discharge on March 18, 1947.

*Comment:* Cure of acute putrid lung abscess with penicillin and sulfadiazine.

*Case 20.* A chronic alcoholic 21 year old Negress entered the Harlem Hospital on February 10, 1947, complaining of cough, fever and pain in the chest of six days' duration. Her sputum was profuse and foul. In April 1946 she had had a chancre which was treated at another hospital with penicillin.

On admission her temperature was 103° F. and she appeared gravely ill. Dullness and large moist râles were elicited over the right upper lobe anteriorly. The admission chest film revealed a 5 cm. cavity with a fluid level surrounded by an area of pneumonic infiltration. She was given sulfadiazine alone for three days without any effect. Thereafter she was given in addition 100,000 units of penicillin every three hours. On February 19, the temperature dropped by crisis and the sputum and cough disappeared. A chest film of February 21 showed the abscess to be half its original size and the pneumonic reaction had disappeared. On February 28 no cavity or pneumonic reaction could be noted. On February 25 a single sputum was positive for acid-fast bacilli; but because three sputa have been negative since and the lungs show no evidence of disease, we feel the positive report was due to clerical error. Bronchography was attempted on March 7, 1947, but she failed to cooperate.

*Comment:* Complete disappearance of large pulmonary abscess with penicillin and sulfadiazine.

As shown in table 1, 19 of 21 cases treated recovered and showed complete roentgenologic resolution of the lesion. One patient left against advice

TABLE I

Table Showing Results of Treatment in 21 Patients with Acute Putrid Lung Abscess with Penicillin and Sulfadiazine

No.	Patient	Sex	Age	Admission	Lesion	Temperature Returned to Normal and Clinical Symptoms Abated in	X-Ray Resolution in
1	T. J.	M	49	10/21/44	L.L.	5 days	37 days
2	I. R.	F	35	4/23/45	L.L., R.L.	10 days	59 days
3	L. M.	M	38	5/ 5/45	R.L.	7 days	65 days
4	A. P.	M	21	7/19/45	R.L., Interlob.	2 days	Interlobar Exudate
5	W. B.	F	28	7/20/45	R.L.	3 days	31 days
6	H. H.	F	37	11/10/45	R.L.	5 days	19 days
7	S. M.	M	41	12/12/45	L.U.	4 days	59 days
8	J. S.	M	26	12/30/45	R.U.	4 days	47 days
9	H. L.	M	54	1/ 6/46	R.U.	4 days	68 days
10	B. S.	M	32	2/18/46	L.U.	8 days	78 days
11	T. F.	M	32	6/10/46	R.U.	35 days	64 days
12	T. G.	F	27	6/16/46	R.U.	11 days	41 days
13	W. M.	M	36	8/14/46	R.U.	4 days	43 days
14	H. R.	M	36	9/ 8/46	R.L.	6 days	23 days
15	J. D.	F	26	9/21/46	R.L.	5 days	30 days
16	A. T.	F	24	12/ 9/46	R.L.	6 days	37 days
17	E. M.	F	24	12/15/46	R.L.	2 days	40 days
18	A. B.	F	36	1/ 5/47	R.L.	2 days	30 days
19	L. B.	M	29	2/ 8/47	L.U.	3 days	31 days
20	R. L.	F	21	2/10/47	R.U.	6 days	18 days
21	E. V.	M	56	1/ 6/47	R.U.	8 days	29 days Died of Brain Abscess 2/15/47

with an interlobar exudate between the right middle and lower lobes. Another patient, who will be reported in detail elsewhere, died with meningitis; and an autopsy revealed purulent meningitis as well as a fetid abscess in the left frontal lobe of the brain, but no evidence of putrid lung abscess.

The distressing symptoms abated, and the temperature returned to normal in two to 35 days after the beginning of the treatment. The average for the group was six days. Roentgenographic clearance of the lesion was noted in 18 to 78 days, with an average for the group of 42 days. The right lower lobe was the seat of the abscess in nine cases, and the left lower in one case. The right upper lobe was affected in seven cases, and the left upper in three. One patient had abscess formation in both the right and left lower lobes.

There were two recurrences among the 21 patients whose acute putrid abscesses had cleared under treatment. In one (case 12), an epileptic young woman, the new abscess recurred within five months in the lobe originally involved. She did well again with penicillin and sulfadiazine. The new abscess has almost completely disappeared, but there is still a linear band of radio-opacity at the base of the upper lobe and she is still under observation. In the second patient (case 10), a chronic alcoholic, the abscess recurred nine months after it had cleared. He claimed to have been ill over two months before his second admission. Penicillin failed to clear this chronic abscess, and the patient refused surgical treatment.

There was also a 36 year old Negro with putrid abscess in the right upper lobe. He did well with penicillin but refused further intramuscular injections before the lesion cleared. His abscess became chronic, but he was treated successfully with pneumonostomy and left the hospital five months after admission.

A 49 year old Negress, who claimed that she was ill for only three weeks with fever, cough and foul sputum, was found to have a markedly shrunken and fibrotic left lung with two oblong cavities in the upper lobe. It was felt that she had chronic abscess formation. Prolonged treatment with penicillin resulted in some clearing of the perifocal infiltration, but the cavities persisted and she refused surgical intervention.

## DISCUSSION

The increase in our knowledge of the pathogenesis of acute putrid lung abscess in the past two decades has led to universal recognition that this disease is a primary clinical and pathological entity. Once considered a frequent complication of lobar pneumonia, it is now well established that this concept is not supported by critical investigation.

At the Harlem Hospital, where for the past 20 years we have treated more than 400 cases of pneumonia yearly, putrid abscess of the lung was one of its rarest complications. Indeed, in the few doubtful cases we observed

in our wards and elsewhere, the diagnosis of pneumonia instead of abscess was made because fetid cough and expectoration were overlooked or were slow in coming, and chest roentgenograms were not routinely used.

The monumental work of Coryllos and Birnbaum,<sup>5</sup> showing that bronchial and bronchiolar obstructions are respectively the true causes of lobar and lobular atelectasis, contributed greatly to our understanding of certain aspects of pulmonary pathology. As a result of their observations, we know that the circulation in any lung segment has a direct relationship to its ventilation and drainage; and any area deprived of its ventilation, as is inevitable when bronchial obstruction and atelectasis supervene, suffers a corresponding loss of circulatory efficiency.

Cohen<sup>6</sup> and others have shown that when noxious material containing pathogenic anaerobic bacteria is aspirated into a small bronchus, the segment of the lung drained and ventilated by this bronchus can become the seat of a putrid abscess. It is reasonable to assume that the growth of the anaerobe is greatly encouraged by the local anoxemia in the atelectatic area distal to the point of bronchial obstruction.

While the aspiration of foreign bodies may cause putrid lung abscess in all age groups and endobronchial tumors in those usually past middle age, most lung abscesses are primary clinical and pathological entities and can develop in apparently healthy individuals. Severe alcoholics, and particularly those unconscious or stuporous following epileptic seizures and anesthesia, obviously are more prone to suffer from this disease.

The size of the abscess in no way affects the method of its care. A large abscess with a wide fluid level is not necessarily the result of extensive necrosis of the lung tissue involved. It is more often due to local obstructive emphysema. The weakened interalveolar septa may be ruptured by the increase in the pressure of the inspired air that cannot be expelled because of the partial bronchiolar obstructions secondary to inflammatory edema. That the lung segment involved is distended by the air under pressure is suggested by the almost geometrically perfect semicircle which forms the upper limit of the abscess, a phenomenon that does not support the presence of extensive destruction of tissue throughout the involved area.

Moreover, the rapid disappearance of the supposed large necrotic cavity, often within a few days after treatment is started, cannot possibly be due to rapid healing and restitution of the local structure. It can be more logically explained by the recoil of the distended segment of the lung once the bronchial obstruction due to inflammatory edema has been reduced by the action of the antibiotic, and normal ventilation and drainage reestablished.

Our experience has shown that it is of utmost importance, if satisfactory results are to be obtained in cases with acute putrid abscess, to continue the combined administration of penicillin intramuscularly and sulfadiazine orally, not only until all toxic and local symptoms have disappeared, but until the chest film shows no abnormal shadows in the segment of the lung involved.

## CHRONIC PUTRID LUNG ABSCESS

It is different in the case of chronic lung abscess. Here the lung and bronchi have been converted by the reaction to the prolonged putrid infection into a maze of fibrosis, multiple hard-walled cavities, bronchiectasis, atelectasis, and chronic pneumonitis, so that restitution to the normal cannot be hoped for with medical care. Often nothing short of lobectomy or pneumonectomy will save the life of the patient. Nevertheless, the combined penicillin and sulfadiazine administration was of inestimable value in the cases who were treated at the Harlem Hospital. It lessened toxicity, prevented further septic and metastatic foci, often cleared the surrounding pneumonitis, and improved the general condition of the patients so that they were better able to withstand the extensive operative interference indicated to bring relief.

## SUMMARY

1. Spontaneous recovery was noted in only 11 per cent of our 70 patients with acute putrid lung abscess.

2. Complete symptomatic and radiographic recovery was attained in 19 of 21 such cases treated with penicillin and sulfadiazine.

3. One patient died of a brain abscess, although his lung had cleared.

4. There were two recurrences of the lung abscesses; one in a girl who had frequent epileptic seizures, and the other in a severely alcoholic young man.

5. Abscess cavities of small and large dimensions disappeared with this method of care. The size of the abscess is most often determined by the degree of coexisting obstructive emphysema, rather than extensive local necrosis.

6. The salient feature in this method of treatment is the continuation of the administration of penicillin and sulfadiazine, not only until all toxic and local symptoms have disappeared, but until the chest roentgenogram shows no abnormal shadows in the segment of the lung involved.

7. Although no recoveries were noted in cases with chronic putrid lung abscess with this method of care, eight of 10 such patients became less toxic by virtue of the partial or complete clearing of the coexisting pneumonitis, and were better able to withstand the extensive surgical interference usually indicated.

8. In view of our experience, the concept that patients with acute putrid lung abscess require early surgical intervention deserves drastic revision.

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# CLINICAL EVIDENCE OF SENSITIVITY TO GONADOTROPINS IN ALLERGIC WOMEN \*

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THE concept that women may become sensitized to the hormones secreted by their own endocrine glands has occurred to a number of observers widely separated in time, place and viewpoint. For example, Finch<sup>1</sup> in 1938, and later (1940), published his finding that the nausea and vomiting of early pregnancy are allergic in origin and that they can be relieved by desensitization with a hormone derived from corpus luteum. My earlier reports on sensitivity to gonadotropins,<sup>2</sup> and on the technic of testing and the results of treatment with a preparation of gonadotropins,<sup>3</sup> appeared in 1942 and 1943. Zondek and Bromberg,<sup>4</sup> writing from Jerusalem in 1945, reported their investigation of allergic sensitivity to the steroid sex hormones. They dissolved these crystallized steroids in purified olive oil. Their positive reactions to intradermal testing with the steroids so dissolved were not the familiar wheal and flare; they were delayed, appearing from three to 48 hours after injection.

This test with steroid hormones in oil is rather inconvenient, and it is not easy to interpret. Thus, Waldbott<sup>5</sup> remarks, "In contrast with the observations of Zondek,<sup>8</sup> skin reactions with extracts of estrogenic substances were inconclusive upon intracutaneous testing." In the same article he states that 47 out of 148 asthmatic females of menstrual age gave a history of having had an aggravation of their allergic symptoms before their periods. In his summary he lists "sensitivity . . . to endocrine products (premenstrual aggravation!)" as among the most important causes of intrinsic asthma. There are many reports of sensitization to insulin. It seems reasonable to accept sensitivity to hormones, for which Zondek proposes the term "endocrine allergy," as a clinical entity.

This communication records two years' further experience in the use of the water soluble gonadotropins along the lines described in my preliminary report. In the hope that it would be of service in cutting down the recurrent disability of many women employed in Arizona's war industries, that report was published locally. Hence, it seems proper to quote from it freely, the more so because the methods and findings then recorded are supported by later work.

My interest in this subject was engaged through accident. An allergic woman patient suffered from menorrhagia and metrorrhagia. Synapoidin was administered intramuscularly and severe shock resulted. The patient recovered, and it was found that an immediate strongly positive reaction to

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an intradermal test with a 1:5 dilution of Synapoidin occurred. This woman, whose allergies had been thoroughly studied, was not sensitive either clinically or by skin test to any meat protein or animal emanation. Passive transfer tests, using non-allergic male recipients, were strongly positive to diluted Synapoidin. Control tests on numerous allergic individuals showed that males, female children below the age of puberty, and the majority of women reacted negatively to this test. Because of the probability that other allergic women might be similarly sensitized, a report<sup>2</sup> of this case was published. Clinical desensitization of this patient was then attempted, using the test dilution intradermally in treatment. Normal menstruation was restored.

Thereafter the test with 1:5 Synapoidin was made routinely on all females between the ages of 12 and 60 who were tested or treated for allergic disease. They had sought relief from various allergic ailments, chiefly from asthma but none specifically from premenstrual headache or tension. The test was, as before, 0.02 c.c. of a 1:5 dilution of Synapoidin, intradermally. The diluent was 5 per cent glucose (Unger's formula), the same diluent used for other allergens. Only those reactions with typical wheal, flare and itching were recorded as positive. In the course of six months, 118 women reacted negatively to this test; 25 others reacted positively. These latter when questioned related various complaints connected with or preceding their monthly periods.

The complaint most often heard was of headache, usually of the migraine type, but not necessarily a classic hemicrania. Usually this was accompanied or preceded by other unpleasant phenomena, such as malaise, vaguely localized pains, digestive disturbances and vertigo. Emotional instability, depression, insomnia and temperamental change were frequently reported, sometimes by a member of the family. Two girls had premenstrual exacerbation of acne. These manifestations, varying in kind and degree, were present in some cases as long as a week before they were ended by the menstrual flow. Most of these women said that, of course, their asthma (or whatever allergy had brought them under treatment) was worse at that time. They seemed to regard this periodic exacerbation as natural and inevitable, a part of the penalty of their sex.

Since most of the women reacting positively to Synapoidin required treatment for other allergic ailments, it was convenient to administer the gonadotropin at the same time. The initial test dose was cautiously increased, and for the reason that a potent biologic agent was being used, the dose was kept consistently low. Synapoidin was always injected separately, so that the local reaction could be observed. In most cases it was vigorous.

The results of treatment in this preliminary group were favorable, especially in the relief of premenstrual headache and tension. The schoolgirls with premenstrual acne showed noticeable improvement. One girl with prepubertal exacerbation of a lifelong asthma was improved (later, normal

menstruation was established). The therapy was so helpful to the limited number of patients concerned that a preliminary report<sup>3</sup> was made.

Since that publication 81 additional patients reacting positively to the intradermal test have been observed and treated. Many of these women were referred, but none by gynecologists. Consequently such conditions as pruritus vulvae have not been encountered. The cases of this second series differ somewhat from those of the first. Sundry complications such as infection and the mutilation resulting from radical surgery have been encountered. The presenting symptoms have been more severe and relief has been less easily accomplished. While most of these women can be included in the group suffering from premenstrual distress, some of the clinical pictures were atypical, requiring the therapeutic test for their diagnosis.

As one listens to the histories of a larger number of these women, one's conviction grows that their functional disorders, varied and diverse though they may be, are all parts of one clinical complex and attributable to a common cause. Thus, the women who complained of headache, which might range in intensity from a dull discomfort to a blazing migraine, were found on questioning to have more or less digestive disturbance as well. Those whose chief woe was "nervousness," running all the way from an irritable grouch to a week of weeping, had also some headache, and so on. The pattern varied with individuals and the individual pattern varied from time to time, yet all the patients had something in common. Freed's<sup>5</sup> suggestion that the entire complex be given the comprehensive name of premenstrual distress has merit.

#### MATERIALS AND METHODS

Synapoidin (Parke, Davis & Co.) is a "gonadotropic preparation . . . obtained by combining chorionic gonadotropin (Antuitrin-S) with gonadotropic hormone extracted directly from the anterior pituitary." It has been shown that in laboratory animals "the combined hormones as contained in Synapoidin have a gonad-stimulating effect several fold greater than the components administered separately." The preparation is standardized in "Synergy Rat Units," based on the minimal dose required to produce a five-fold increase in the ovarian weight of sexually immature female rats. As marketed, it contains 15 such units to the c.c.

Several other preparations of gonadotropin were tried in approximately parallel dilutions. Any of these gonadotropins may, in an occasional subject, induce a blanching of the skin at the site of injection. Perhaps this is caused by the presence of a trace of posterior pituitary in the extract. This blanching soon disappears and it has no clinical significance, although it may retard the appearance of a positive reaction. This effect was observed less frequently with Synapoidin, which also elicited stronger and more uniform reactions. For these reasons its use has been continued.

The active allergen appears to reside in the anterior pituitary hormone or in its combination with chorionic gonadotropin. Antuitrin-S, the chorionic component, was used as a control on 25 women who reacted positively to Synapoidin. Only two relatively weak positive reactions occurred, and no further tests were made with Antuitrin-S. This resembles the experience of Zondek and Bromberg, who mention encountering only "one case of sensitivity toward chorionic gonadotropin." They used Korotrin (Winthrop).

### DOSAGE

Synapoidin in 1:5 dilution was used throughout this series. Where doses are stated, this dilution is to be implied. The initial dose was always that of the positive test, 0.02 c.c. No patients were treated who did not react positively and definitely to this test. Because of experience gained in the earlier work, in every case the attempt was made to adjust the dosage to the individual's requirement as determined clinically, and *no attempt was made to increase the dose beyond the quantity needed to produce symptomatic relief*. In only two cases was the maximum dose of 0.30 c.c. exceeded. It was observed that older women generally tolerated and required a larger dose than their juniors.

As a rule two doses were given in each menstrual month, the first about one week after bleeding ceased, the second a week later. When menses were irregular or delayed, one dose a week was administered until the normal period was reestablished.

All injections were strictly intradermal.

### RESULTS OF TREATMENT

In all, and counting the pioneer case, 107 women showing evidence of sensitivity to gonadotropins by intradermal test have been observed and treated for periods ranging from three months to three years. In the series of 81 additional cases that constitute the material of the present report, the results were as follows:

1. *Premenstrual distress*. These women, constituting some 60 per cent of the case material, presented the syndrome of premenstrual tension and headache with its concomitants in varying combinations and degrees of intensity. Most of them had other allergies. Serious organic complications were unusual. The greater number had not sought medical relief from their discomfort, believing that nothing could be done about it; the few who had seemed to hold a like opinion.

Total cases, 49. Relieved, 33; improved, 9; unimproved, 6; not treated, 1. Average dose, 0.09 c.c. twice monthly.

Comment: In this group there was ready response to treatment. When relief was attained and continued over a few periods, it continued for several months without further gonadotropic medication.

2. *Premenopausal group.* These were women who had experienced a sharp increase of their allergic symptoms at the approach of the climacteric. With one exception they were asthmatic. None had as yet manifested the vascular and nervous indications of the menopause. All had received estrogenic medication without relief. Treatment directed toward their known allergies, formerly not without success, no longer controlled their symptoms. Essentially the same treatment supplemented by a suitable dosage of gonadotropin brought about substantial improvement in the majority of the cases. In two instances, it made the difference between invalidism and a nearly normal mode of living.

Total cases, 10. Relieved, 4; improved, 4; unimproved, 2. The dose varied widely, from 0.03 to 0.30 c.c.

Comment: Because of their age, the presence of complications and the existence of irreversible organic damage, the treatment of this group was difficult. Some of them required and tolerated a relatively large dose. This raises the question of whether the beneficial effect was due to ovarian stimulation, rather than to a specific desensitizing action. This will be discussed later.

3. *Prepubertal.* A girl, aged 12 years, whose chronic asthma had gone out of control as puberty approached was promptly relieved when 0.05 c.c. of diluted Synapoidin was added to her regular treatment at weekly intervals. Normal and uneventful menstruation began two and one-half months later.

Comment: There was a girl with a similar history in the series reported earlier.

4. *Acniform facial eruption*, during the premenstrual week; four cases. Three school girls, who also had hay fever, were improved; one had permanent relief without scarring. Their average dose was 0.15 c.c. A woman of 38 years, with a similar eruption modified by roentgen-ray, was not benefited by a full dose of gonadotropin, supplemented by vaccine and staphylococcus toxoid.

Note: These girls were sternly enjoined to stop pricking and squeezing their pimples.

5. *Urticaria*, and an undiagnosed condition. There were three cases of urticaria, all referred. All were found, when they could be tested, to react positively to Synapoidin; no other positive reactions could be demonstrated. All recovered in time, but the effect of the gonadotropin therapy is doubtful. The dosage varied from 0.12 to 0.30 c.c. The fourth patient in this group, reported as a medical curiosity, could not be diagnosed by the several doctors who examined her.

*Case 1.* Mrs. M. M., aged 24 years, referred by Dr. W. H. Woern, had always been healthy, and her periods were normal. Her only complaint was that for several years she had been annoyed at times by nasal stuffiness and a running nose, and this was not affected by place or season. Her present illness had begun abruptly three days before her menstrual period with what she thought was a feverish cold. Next morning her face began to swell, and in a few days the swelling involved the neck and

the extremities. She thought that she had sinus infection, but Dr. Woern found no evidence of it; instead, the nasal mucosa was edematous and irritable, and the usual local applications made it worse. She was referred for diagnosis and treatment.

She looked like a person with nephrosis, but she was not sick. Other than a moderate eosinophilia, laboratory tests revealed nothing abnormal. An elastic swelling that did not itch involved the face so that she could hardly see out of her eyes. On the neck and extremities it was of lesser degree. The rest of her skin was clear.

She was doing war work while her husband was overseas. Patch tests with the usual substances, plus dusts and chemicals from her place of employment, were negative. The routine tests with allergens were also negative by intradermal injection; the only positive test was to diluted Synapoidin. This was given twice a week, in a dose that finally reached 0.40 c.c., more than any other patient in this series tolerated. The edema gradually subsided, and after five weeks, during which treatment was interrupted by a normal menstrual period, the swelling disappeared. Treatment was stopped, and next month there was a mild recurrence of symptoms, which subsided after two doses. A year later, a follow-up letter reported no further trouble. Her husband was home from the wars. Again, the effect of treatment is in doubt.

6. *Dysfunctional bleeding*, with irregularity of menstrual time. Three cases, one so serious that hysterectomy was about to be done. All were relieved and normal menstruation at 28 day intervals was restored. All these women have other allergies. Average dose, 0.20 c.c., two or three times monthly, continued until relief.

7. *Vicarious menstruation*. One case. Mrs. C., a divorcee, aged 29 years, nullipara, had come to Arizona with moderately advanced tuberculosis. In due course her disease was apparently arrested, but she had been kept on the rest cure for a year longer because of irregularly recurring episodes of hemoptysis. She had no other signs or symptoms of tuberculous activity.

Inquiry disclosed that in her home state, but not in Arizona, she suffered from hay fever. Her family history showed allergic disease. Her menses had begun when she was only 10 years old; the periods had been irregular, and always preceded by several days of malaise and distress. She said that the only way she could tell when a period was coming was by the preliminary sickness. When tested, she reacted positively to eastern pollens and to Synapoidin. The latter was used in 0.20 c.c. doses once a week. After four doses an uneventful menstruation occurred, and the same dose was administered once a month thereafter. For the first time in her life, this woman's menstrual periods were regular and normal. Gradually she resumed her usual mode of life. The improvement in her general health was striking. No further hemoptysis occurred.

8. *Perennial allergic rhinitis* with premenstrual exacerbation. Nine cases, all referred by specialists in diseases of the nose and throat. On routine testing, seven reacted only to Synapoidin; two were sensitized also to house dust.

Results: Relieved, 4; improved, 4; unimproved, 1. Average dose 0.16 c.c.

Comment: Evaluation of the results of therapy in this group is impossible. All had failed to obtain more than transient relief from local treatment, and it was discontinued for the period of observation. All were advised to quit using nose drops. All received Synapoidin in medium dosage twice in the intermenstrual interval. The two who reacted to house dust got that as well, and the others were given intradermal doses of a stock vaccine to which they reacted sharply. While most of them reported considerable relief, the rôle of gonadotropins, either in etiology or in therapy, is open to question.

### PSYCHIC INFLUENCES

It is well known that emotions may alter the functions of the adrenals and the thyroid; it is reasonable to assume that other endocrine glands can be similarly affected. This may have happened in some of the cases here reviewed. For example, among the failures in group 1, there were two badly adjusted old maids; another woman hinted that her marital life was unsatisfactory. One of the three urticarias (group 5) was distracted by the loss of a baby, another had recently left her husband, or vice versa. Psychic states such as these, if they modify in quantity or quality the endocrine secretions, may have had some effect on the incidence of symptoms and the results of treatment. One woman was turned over to a psychiatrist when the examination was completed; perhaps this should have been done with a few others. In my experience it is most useful to take the patient's history personally. The examiner becomes acquainted with the patient and her individual attitude and problem; the patient acquires confidence in her physician. The psychic factor is bound to be active, and it had better be made to operate in a helpful way. Aside from this simple procedure no attempt at psychotherapy was made. In fact, the management was designed to minimize the effect of suggestion, so far as that can be done when any treatment is used.

### DISCUSSION

This paper is a record of clinical observations in private practice. Only the initial case, reported earlier, was thoroughly worked up. In that case the postulates were satisfied and it can be asserted that the patient was allergically sensitized to a preparation of gonadotropins. It would not have been proper to burden the succession of apparently similar patients with the considerable expense of laboratory work necessary for scientific proof.

No series of controls is presented; Synapoidin was not administered in parallel dosage to an equal number of allergic females who reacted negatively to the skin test, although such were readily available. Because of the delicate balance of the menstrual mechanism, such use of a potent gonadotropin was considered unjustifiable. Also, there was the theoretical possibility that sensitivity to the hormone might be induced in persons not previously so afflicted.



The word "desensitization" is purposely avoided in this article. Early in this study it was learned that desensitization, in the sense of inducing tolerance to a large dose by means of a series of steadily increased preceding doses, is neither necessary nor desirable. The effect of the hormone in overstimulating the ovaries soon appears, in the form of lower abdominal pain, engorgement of the breasts and disturbance of the menstrual flow. Injection into the skin, a shock organ, is serviceable in keeping the dosage low. With this technic it is possible to obtain protection against an offending allergen with a fraction of the quantity required by other methods of administration. This statement is based on the author's long experience with intradermal pollen therapy. Incidentally, Zondek's <sup>4</sup> successful treatment of pruritus vulvae by the inunction of minute doses of estrogen applies the same principle. What has been said before is repeated for emphasis: *The best results were obtained by a low dosage, adjusted to the individual's tolerance and requirement, and not increased beyond the point at which relief occurred.*

Up to a certain point which varies with the individual, the endocrine product here discussed behaves exactly like any other allergen in a sensitized subject. The local reaction is the same; it is easy to produce constitutional reaction in its varying degrees. With larger doses the effect may be that of hormone overdose, and the threshold levels of these two intolerances are not the same. When the dosage is kept safely within tolerance, this dual quality is again apparent. For example, the premenstrual exacerbation of an ailment commonly recognized as allergic is prevented, and so is the syndrome of premenstrual distress, which many believe to have an endocrine origin. In the many successful cases there appeared to be a restoration of the balance between the gonadotropic hormones and their natural physiologic antagonists. The women reported not only relief but a notable improvement in their general health. And when this desirable result was obtained, it persisted for several months without further medication in cases of simple premenstrual distress with associated allergies. This was accomplished with an average dose of about one-third of what the manufacturer calls a Synergy Rat Unit, or from 2 to 4 per cent of the recommended intramuscular dose. The positive skin reaction must have some significance. The available evidence warrants no conclusions, but it does suggest certain questions. For example, does intradermal administration, which amplifies the effect of allergens, likewise increase the potency of hormones? Are women who are clinically sensitized to endocrine products also over-sensitive to the hormonal effect of those same products? And might it be possible that premenstrual distress is a localized allergic manifestation, with capillary permeability and edema, like hives? Problems of this sort must be left to those specially qualified and equipped for research.

The results in this series are generally parallel to those obtained by Zondek with steroids in oil, and by Freed and others who used androgens as antagonists of estrogen. These similar results reached by differing

modes of therapy are not incompatible; probably they represent different avenues of approach to the complex reactions of the reproductive cycle. It would seem that the gynecologists, with the choice of three successful methods of treatment, are now in a position to make a substantial subtraction from the sum total of human misery. The allergists, if so inclined, can easily verify or disprove the existence of sensitivity to combined gonadotropins by including a 1:5 dilution of Synapoidin in their test sets. Also, if the dosage is kept below the tolerance limit of the individual patient, they should have no trouble in duplicating the favorable results. It is my firm conviction that women sensitized to gonadotropin respond better to treatment for other allergies when the hormone sensitivity is controlled. Even if this were not true, the physician would be well rewarded by the spontaneous expressions of gratitude on the part of the patients and their families. Apparently the correction of disturbed menstrual function is of more importance than some of us have realized.

### SUMMARY

The author's earlier publications on this subject are reviewed. The first<sup>2</sup> reported allergic shock caused by Synapoidin in a patient who later was proved to be sensitized to that gonadotropic preparation. The second<sup>3</sup> was the preliminary report of the symptoms and treatment of 25 women screened out of an allergic clientele by positive reaction to intradermal testing with combined gonadotropins. The results of treatment were encouraging.

This communication is based on the records of 81 cases similarly selected. While the greater number suffered from premenstrual distress together with various allergic ailments, asthma being the commonest, the clinical manifestations of others were different and sometimes atypical.

The method of test and treatment has remained unchanged. Synapoidin (Parke, Davis & Co.) in 1:5 dilution was used in test and treatment. The test was 0.02 c.c. intradermally. Only those women who showed a definite immediate positive reaction were treated.

Desensitization, in the sense of inducing tolerance to a large dose by means of a series of ascending doses, was found to be neither necessary nor practicable. The best results were obtained by a low dosage, adjusted to the individual's tolerance and requirement and not increased beyond the point at which relief occurred.

The results of treatment were good in premenstrual distress; favorable in the premenopausal group; excellent in dysfunctional bleeding; fair in a few cases of premenstrual acne; inconclusive in perennial allergic rhinitis; doubtful in urticaria, and poor in the presence of anxiety states and neurosis.

In favorable cases a dual effect was observed. Premenstrual exacerbation of recognized allergic disease, such as asthma, was prevented and the syndrome of premenstrual distress was likewise abolished. Once esta-

blished, this relief persisted for months without further medication with gonadotropins.

Women clinically sensitized to gonadotropins responded better to treatment for their ordinary allergies when the hormone sensitivity was controlled. Even in the fractional doses employed, the gonad-stimulating effect of Synapoidin was occasionally observed, but in most cases its clinical behavior was that of an allergen.

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# OBSERVATIONS ON RELAPSES IN PERNICIOUS ANEMIA \*

By EDGAR JONES, M.D., F.A.C.P., CLIFFORD C. TILLMAN, M.D., and  
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IN the fall of 1945 and winter of 1946 liver extract was discontinued on 12 patients with pernicious anemia who were attending the out-patient department of Vanderbilt University Hospital. There were seven males and five females in the group. Two of the men were Negroes. None had evidence of neurological disease. All of these patients were regarded as being adequately treated. The total amount of liver extract which had been injected during the year prior to withdrawal of treatment varied from 420 to 1020 units and had been given at intervals of three to four weeks in the majority of instances.

The average of red blood cell counts made during the year before treatment was discontinued was 4.74 million for the seven men and 4.29 million for the five women. It is to be noted that two of the women averaged a scant 4 million red cells during this period, at times having counts as low as 3.61 million. One of these patients had been given 50 units of liver extract parenterally every two weeks over a period of three years without causing any red cell increase. Thus it is to be assumed that her "normal" level was at 4 million red blood cells or less. No evidence of infection or other disorders known to inhibit response to liver extract was apparent in either of these patients. It is well to recognize that such patients may be encountered during the assay of hemopoietic fractions. In view of the variability of maximum levels under adequate therapy, what red blood cell level is to be taken as indicating relapse? Strauss and Pohle<sup>1</sup> defined hematologic relapse as occurring when two successive red cell counts were 4 million or less. By such standards our two patients mentioned never had gone beyond the relapse range, in spite of very large doses of liver extract. Rather than set any absolute level of red blood cells it appeared to us better to relate relapse to the red cell levels of the individual patient. Obviously a fall in red cell count to 4.0 million has a different significance for a patient with a treatment level of 5.5 million than for one with 4.5 million. We calculated the mean and standard deviation of counts on each individual patient for the last year of liver therapy. Two successive counts on a patient more than two standard deviations below his treatment mean was defined as a relapse. This procedure makes it highly unlikely that the lower counts were due to chance variation and allows each patient to set his own "relapse level" in relation to his previously maintained values.

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By applying these criteria six of the 12 patients had relapsed by April of 1948. Of the seven males five have relapsed; one of the five women. The time required for relapse varied from eight to 18 months. Three of the patients showing hematologic relapse recovered their blood values spontaneously for a few months, only to have a progressive relapse follow. The time of the first relapse is used in this report. This is illustrated in charts 1 and 2.

The six patients who have not relapsed have been from 26 to 29 months without liver extract. Chart 3 shows the course followed by a patient who did not relapse. None of the entire group of 12, whether relapsed or not, has developed complaints of any sort. All have been followed closely with examinations for evidence of neurological disease, glossitis and diarrhea as well as to their general sense of well being. There have been no changes in weight of significance except for one man of the relapse group who has gained appreciable weight. This long period required for relapse emphasizes the caution required in interpreting the maintenance efficacy of an agent substituted for liver extract, e.g. pteroylglutamic acid (folic acid, PGA).

After this relapse program had been under way for about 21 months it occurred to us that it would be of interest to follow the fecal urobilinogen levels of this group. It has been well established<sup>2</sup> that urobilinogen is considerably increased in the stools of patients with pernicious anemia in relapse

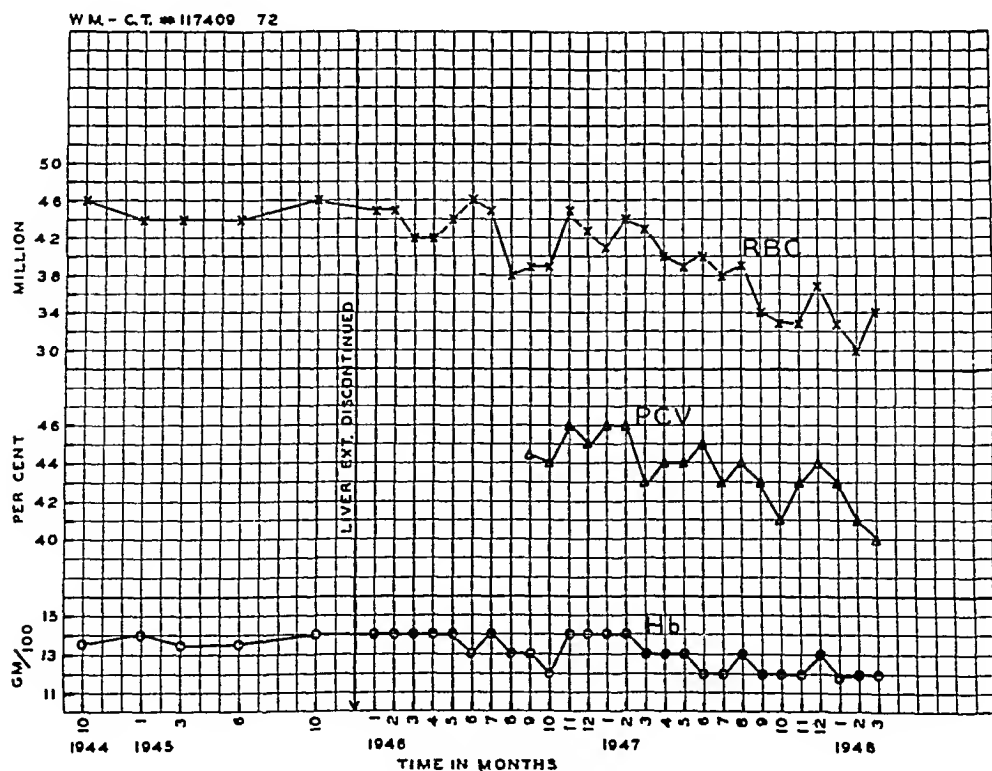


CHART 1. Shows pattern of relapse with a short return to normal levels.

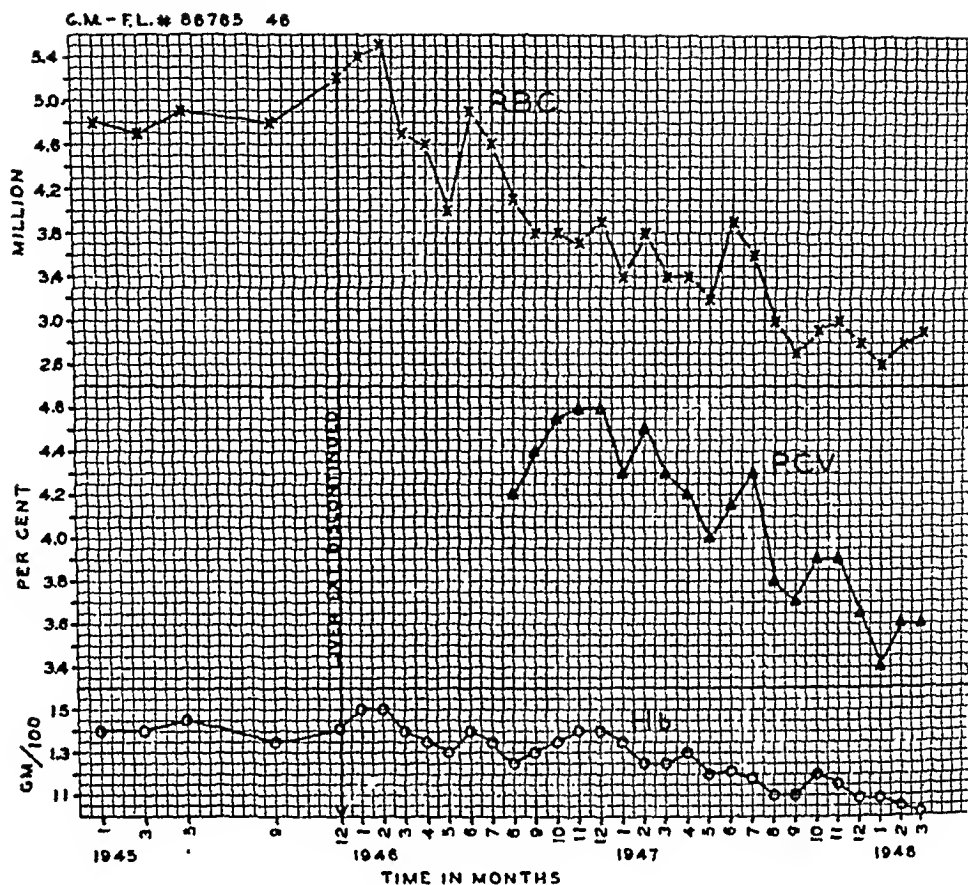


CHART 2. Same pattern of relapse as in chart 1.

and that there is a rapid decrease following the giving of liver and liver extracts. It has also been shown that normal values for urobilinogen are found where there is no anemia.

Fecal urobilinogen was determined by the method of Watson.<sup>3</sup> The majority of determinations were made on stool specimens collected over a period of four days. However, some determinations were made on single stool specimens. We consider single specimens of equal value to four day collections for this purpose since our experience gave us no reason to feel that values of significance were missed by this procedure. Urobilinogen values greater than 300 Ehrlich units per 100 grams of feces were taken to indicate an increase over normal.

Chart 4 shows the relationship between red cell and urobilinogen values. It is to be noted that only where there is anemia is there an increased urobilinogen value.

Chart 5 shows the hematologic course of a man with pernicious anemia who had a good response to parenteral liver extract. He was then allowed to relapse. At this point he was given pterioic acid (chart 6), a part of the pteroylglutamic acid molecule. He obtained an incomplete hematologic response to this material. He was again allowed to relapse at which time he

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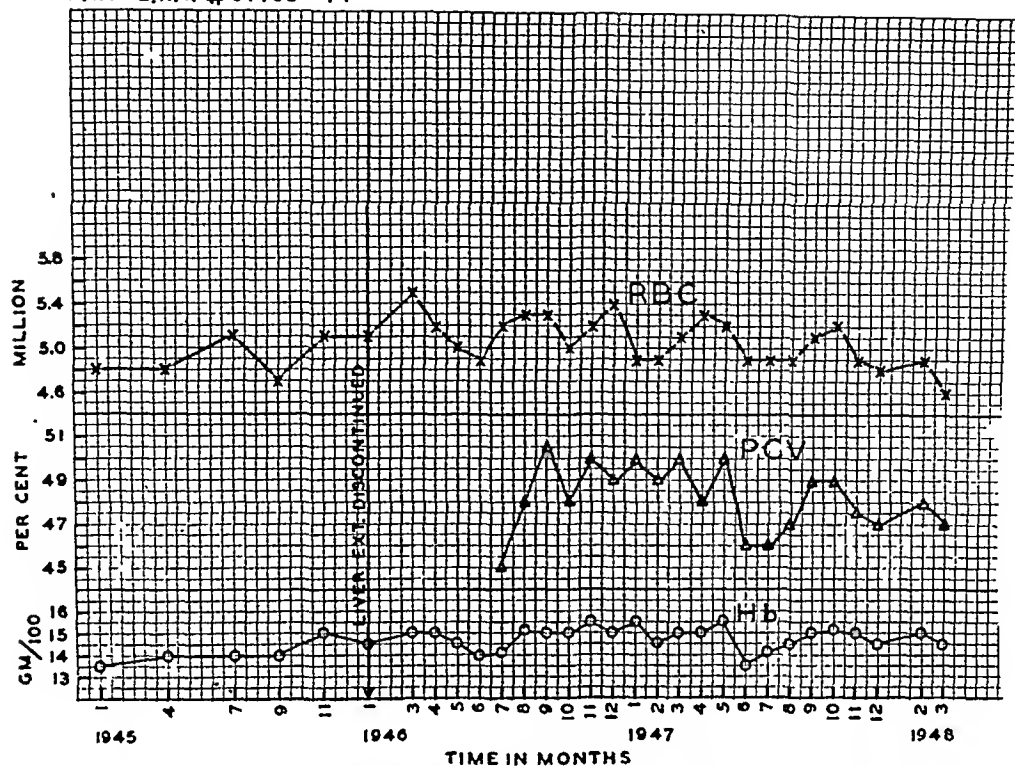


CHART 3. Hematologic findings in a patient who showed no relapse by 26 months.

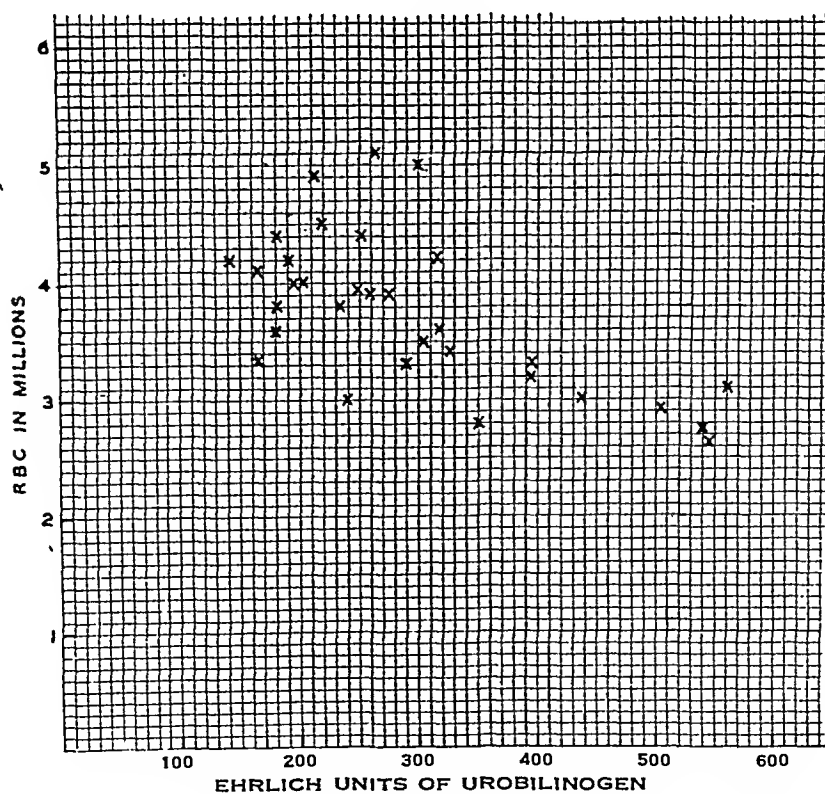
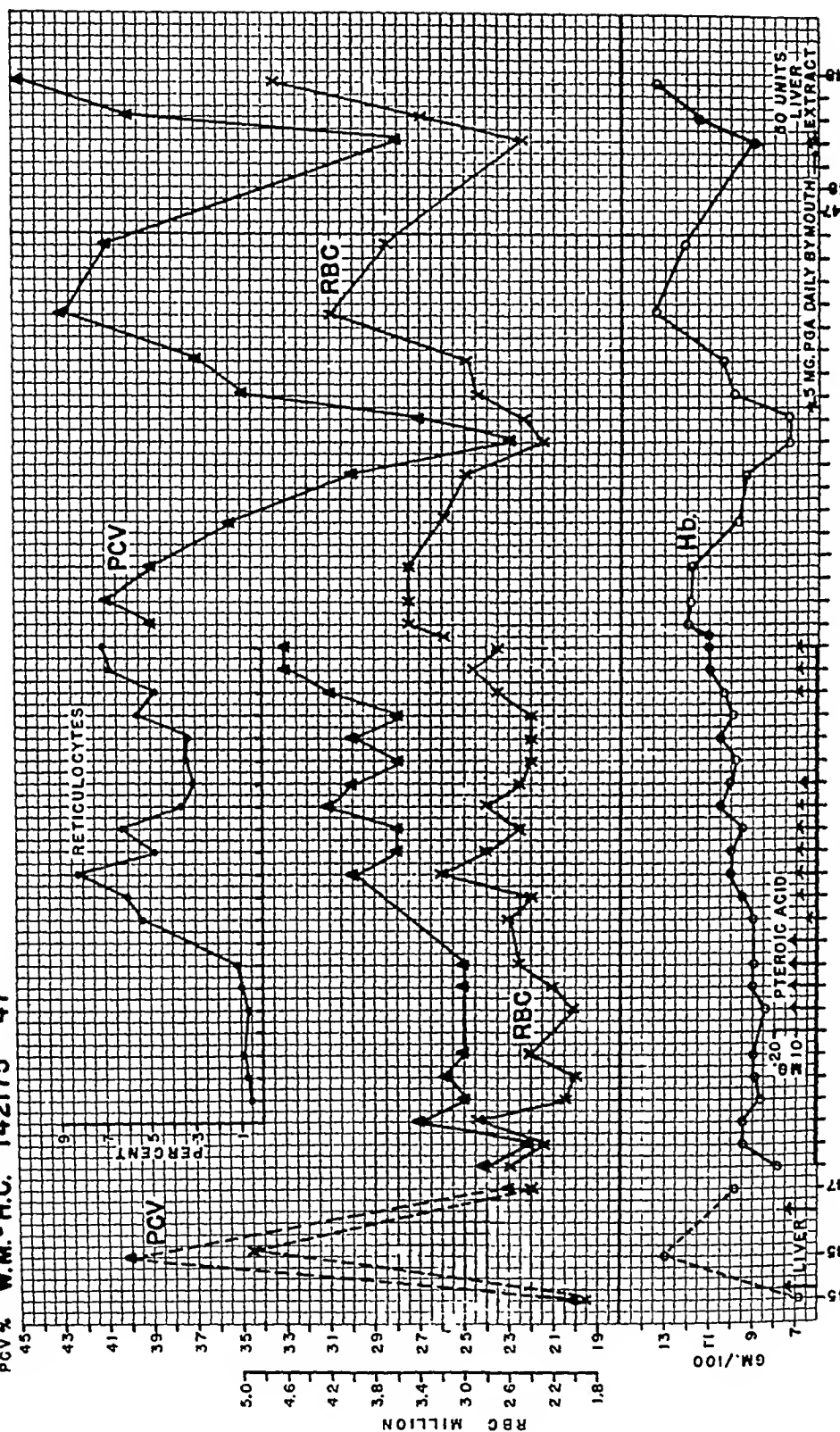
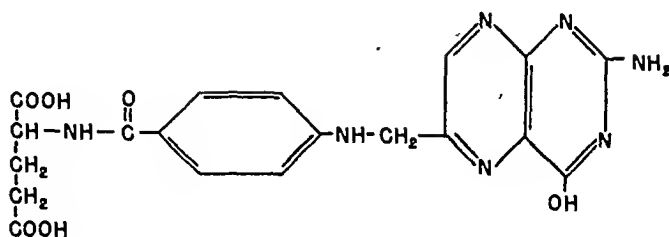


CHART 4. Scatter chart showing relation of red blood cell and urobilinogen levels.

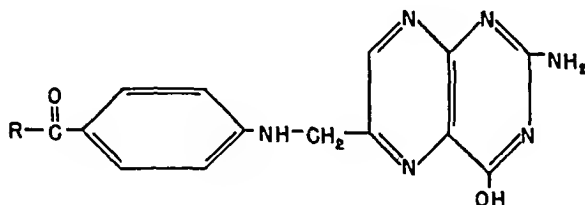
PCV % W.M.-H.C. 142175 47







I.



II.

PTEROIC ACID     R = OH

FERMENTATION FACTOR     R = 3 GLUTAMIC RESIDUES

CONJUGATE     R = 7 GLUTAMIC RESIDUES

CHART 6. Formula for pteroylglutamic acid and its constituents.

was given 5 mg. of pteroylglutamic acid by mouth with an initial good response. However, while receiving PGA in 5 mg. doses daily he exhibited a definite relapse. He was then given large doses of liver extract by injection, obtaining the highest blood values seen at any time during the three year period of observation.

### DISCUSSION

No cause is apparent for the differences in time required for relapse to occur in the 12 patients observed. Certainly there was no correlation between time of relapse and the amount of liver extract given during the year prior to its withdrawal. It is of interest that of the seven men followed five have relapsed, whereas only one of the five women has relapsed. The small number of patients renders this sex difference probably of no significance. It is of further interest that in three of the patients who showed relapse there was a short-lived return to higher than relapse values before sustained relapse ensued.

No neurological manifestations developed in any of the 12 patients during the period of observation. This is of interest in light of recent reports<sup>4, 5</sup> of a high incidence of neurological findings in patients with pernicious anemia who had been given PGA and tends to confirm the suspicion that this new vitamin actually brings about neurological damage.

While high values of urobilinogen in the stools of patients with pernicious anemia in relapse have been observed regularly, it is worthy of note that these increases are shown to begin at a time of only minimal anemia. This further emphasizes the rôle of hemolysis in the pathogenesis of this disease.

## SUMMARY

1. Following withdrawal of liver extract six of 12 patients had failed to show hematologic relapse over a period of 26 to 29 months.

2. Eight to 18 months were required for relapse to appear in the six patients exhibiting this.

3. Standards for hematologic relapse are described which relate relapse to the individual patient's blood level before treatment was stopped.

4. The output of urobilinogen in the stools increases early in hematologic relapse and appears to increase as anemia progresses. This indicates that hemolysis becomes operative early in the relapse of pernicious anemia and emphasizes its importance in the pathogenesis of this disease.

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# THE USE OF A NITROGEN MUSTARD\* IN HODGKIN'S DISEASE AND LYMPHOSARCOMA †

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MEDICAL science has profited from the study of agents used in chemical warfare. Investigation into the mode of action of mustard gas revealed a type of action of sulfur and nitrogen mustards which is unlike that of any other chemical agent and resembles in many ways that of roentgen-rays.<sup>1</sup> The effects of the mustards on lymphoid tissue, coupled with the finding that actively proliferating cells are selectively vulnerable to the cytotoxic action of the mustards, led to its use in the treatment of neoplasms of lymphoid tissue. Of the many substances studied, two variants of special importance have emerged: tris ( $\beta$ -chloroethyl) amine hydrochloride and methyl-bis ( $\beta$ -chloroethyl) amine hydrochloride.

This report deals with the therapeutic use of methyl-bis (B-chloroethyl) amine hydrochloride, in two cases of Hodgkin's disease, and three cases of lymphosarcoma.

*Dosage and Method of Administration:* The amount of the methyl-bis compound recommended as a single course is 0.1 mg. per kilogram intravenously on four successive days (a total of 0.4 mg. per kilogram).<sup>3</sup> Subsequent therapy varies with each patient.<sup>2</sup> In the following cases if the clinical response was not satisfactory after two to three weeks and the hemogram was within normal limits, two to four additional injections of methyl-bis were given. The interval between courses of therapy varied from two to 12 weeks.

Nitrogen mustard must be administered only by the intravenous route, taking great care to prevent extravasation of the solution. The solution is freshly made by adding 10 c.c. of normal saline solution to the sterile glass ampule containing 10 mg. of the dry salt. It is necessary that injection be accomplished within five minutes of preparation of the solution because of the rapid hydrolysis which may occur with consequent loss of efficacy. Pain during injection and subsequent thrombophlebitis of the injected vein were frequently noted by us and others<sup>2</sup> during the direct syringe technic of drug administration. This complication, it was found, could be generally prevented when the calculated dose was injected into the rubber tubing of a freely flowing intravenous infusion of glucose or saline solution.

*Toxic Manifestations:* These may be classified as early (within 24 hours of medication) and late. The early toxic effects consist of (a) pain and

\* Methyl-Bis ( $\beta$ -chloroethyl) Amine Hydrochloride.

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We wish to thank Drs. Louis J. Ruschin and Gerald Crenshaw for allowing us to include their cases.

tender induration at the site of injection if the solution escapes from the vein; (b) thrombophlebitis of the vein being used to introduce the medication; (c) nausea and vomiting occurring within one to three hours after injection and persisting for from two to 18 hours<sup>4</sup> and (d) diarrhea during the course of therapy.<sup>3</sup>

The late toxic manifestations result from widespread destruction of hemopoietic tissue and may be observed in the following sequence: (1) lymphopenia, (2) granulocytopenia, (3) thrombocytopenia and (4) moderate anemia.<sup>2</sup> These serious complications almost invariably occur within the first three weeks and make hemograms a necessity for three weeks following methyl-bis therapy.

In our cases all of these complications were observed to some extent while nausea and vomiting after each injection of medication was universal. Follow-up examinations included urinalyses, cephalin flocculation, thymol turbidity tests, icteric index and plasma proteins with A/G ratio and showed no remarkable change in these patients.

#### CASE REPORTS

*Case 1.* A 36 year old white male entered the hospital July 17, 1946, in the terminal stages of Hodgkin's disease. History revealed that he had received repeated roentgen-ray therapy since 1938. In July, 1946, persistent nausea, vomiting, dyspnea, orthopnea and severe pain along the distribution of the right sciatic nerve had developed. Two separate radiological departments felt that further roentgen-ray therapy was not indicated, and he entered Fairmont Hospital for terminal care.

Physical examination revealed a poorly nourished, chronically ill white male in moderate respiratory distress. The temperature was 101° F., pulse 100 and respirations 30 per minute. The blood pressure was 110 mm. of mercury systolic and 90 mm. diastolic. Entrance weight was 120 pounds. Lymph nodes were enlarged bilaterally in the cervical, supraclavicular, axillary and inguinal regions. There was a firm mass 6 by 6 by 2 cm. in the fourth left intercostal space, a mass 6 by 4 cm. in the belly of the left rectus abdominis muscle and a mass 4 by 4 cm. in the right sacral area. The spleen extended to the crest of the left ilium.

Significant laboratory data showed a hemoglobin of 8 grams; roentgenological studies revealed a left hydrothorax, probable pericardial effusion and sclerotic changes in the third lumbar vertebra. Two lymph node biopsies showed the histological picture of Hodgkin's disease.\*

*Course:* Methyl-bis 0.1 mg. per kilogram of body weight per day was given on four consecutive days, beginning August 12, 1946. Each injection was followed by nausea and vomiting, lasting two to four hours. Ten days later all masses had decreased strikingly in size, the appetite was ravenous and the patient was afebrile. However, pain in the distribution of the right sciatic nerve persisted and required aspirin and codeine for relief.

Because of the pain and the gradual reënlargement of the previously described masses, therapy was repeated, beginning September 13. Tumor regression again occurred, but the right sciatic pain became sufficiently severe to require Demerol for relief.

\* Interpreted by Dr. R. J. Parsons.

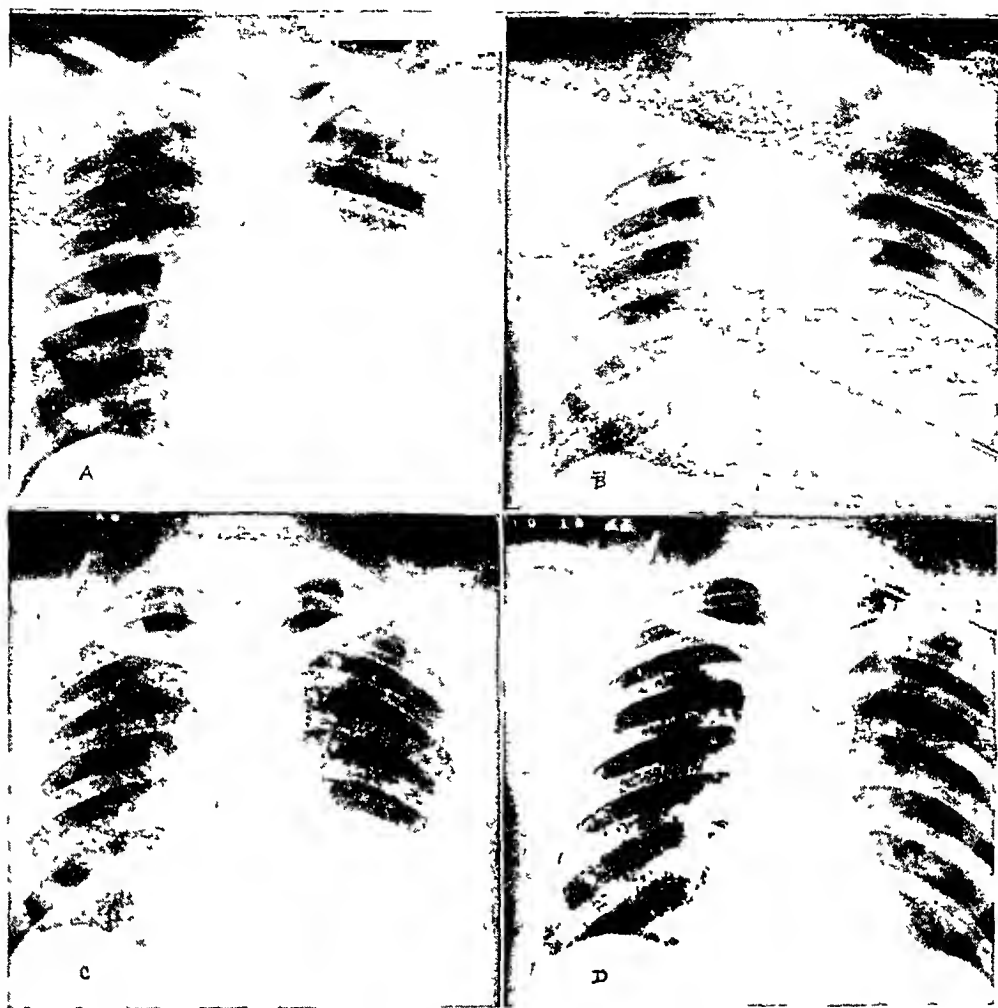


FIG. 1. (Case 1.) Roentgenograms showing effect of therapy on the progress of the mediastinal lesion, pericardial and pleural effusion. "A" represents the pretreatment film. "B" was taken 18 days after first course nitrogen mustard was begun. "C" 30 days after first course nitrogen mustard was begun. "D" 67 days after first course nitrogen mustard, and 35 days after second course. Between July 30, 1946 and October 18, 1947, two courses of the drug were administered.

By October 15, the patient had gained 11 lbs.; a chest roentgenogram was described as normal, but right sciatic pain had increased until it was occasionally necessary to use morphine in addition to Demerol to obtain relief of pain.

A further course of four methyl-bis injections was begun on November 8, and, as no relief was noted, two more injections were given on November 21 and 22. Following this, symptomatic and objective improvement was dramatic; narcotics were discontinued, and the patient discharged to clinic care on December 4, 1946.

Two further courses of methyl-bis were given in January and March, 1947. As of June 1947, the patient has been referred to the roentgen-ray department for therapy to a mass in the left gluteal region. This mass has failed to disappear under methyl-bis therapy. Biopsy of the mass on June 23, 1947 showed extreme fibrosis and numerous cells of the Reed-Sternberg type bordering an area of anemic necrosis. No eosinophiles were found but the lesion was interpreted as a late stage of Hodgkin's disease showing areas of necrosis.\* The physical status of the patient allows him to

\* Interpreted by Dr. R. J. Parsons.

hold two part-time positions. His weight is 162 lbs. (a gain of 42 lbs.), hemoglobin 16 grams per 100 c.c., and white cell count 6600 per cu. mm. with a slight shift to the left and an eosinophilia of 11 per cent.

*Case 2.* The patient, a 25 year old white male, first noted undue fatigue and vague chest pains in June, 1945.

Physical examination revealed only moderate bilateral axillary lymphadenopathy. A roentgenogram of the chest was interpreted as showing a widened mediastinal shadow. A lymph node, removed from the left axilla, showed the changes of early Hodgkin's disease.

*Course.* Roentgen-ray therapy to the mediastinum reduced the width of the mediastinal shadow until October, 1946, when no further response was noted and it was decided to use methyl-bis.

Following the first series of four injections, the mediastinal and axillary nodes slowly regressed in size. A second course of methyl-bis was given in January, 1947. Following each of the courses, lymphopenia and leukopenia were noted, but the count returned to normal within three weeks. As of June, 1947, the patient is symptom-free, shows no recurrence of mediastinal or axillary adenopathy and is gainfully employed.

There have been three cases of histologically proved lymphosarcoma in this group.

*Case 1.* A 69 year old white female was referred for methyl-bis therapy in October, 1946. Her history revealed that her complaints had been controlled by roentgen-ray therapy since 1941, but at the time of referral skin changes prevented further treatment.

Physical examination showed a chronically ill patient. The axillary and inguinal lymph nodes were enlarged and a basket-ball sized mass was present in the right lower quadrant of the abdomen.

*Course.* Two weeks following a course of methyl-bis, the patient had a sense of well-being; the peripheral lymph nodes had markedly decreased in size, and the abdominal tumor was no longer palpable. A leukopenia of 1200 cells per cu. mm. developed by the fourteenth day following therapy, but the leukocyte count returned to normal within one month.

A repeat course of methyl-bis was given in January, 1947, following reënlargement of the lymph nodes and reappearance of the abdominal mass. Clinical and hematologic response was similar to that following the first course.

Following each injection of methyl-bis, nausea and vomiting of three to four hours' duration appeared.

As of June, 1947, the patient appears to be in good health, except for radiculitis of the sixth left thoracic nerve.

*Case 2.* A 51 year old white female was referred for methyl-bis therapy in November, 1946. Her history revealed that she had been receiving roentgen therapy since 1944, but that for the present, skin tolerance had been reached.

Physical examination showed a chronically ill patient with generalized lymphadenopathy. There was 3 plus pitting edema of the left arm and laryngeal stridor.

*Course.* Following a series of four injections of methyl-bis, beginning November 8, there was marked decrease in the lymphadenopathy, decrease in the edema of the arm and disappearance of the stridor.

A return of the previously described signs and symptoms necessitated a repeat course of methyl-bis beginning December 15. Marked improvement again occurred, but the patient died in her sleep January 12, 1947. No autopsy was obtained.

*Case 3.* The patient, a 59 year old white female, entered the hospital March 24, 1947. In February, 1946, a nodule had developed in the left anterior triangle of the

neck and had grown rapidly. In May, 1946, a similar nodule appeared on the right side of the neck and enlarged rapidly. Biopsy of a cervical lymph gland was diagnosed as reticulum-cell sarcoma. Roentgen-ray therapy from July, 1946, through February, 1947, only partially controlled the size of the cervical nodes.

In January, 1947, the patient developed a peripheral facial weakness on the left and experienced difficulty in talking and breathing. At this time she also complained of severe pain in the left side of the neck and face.

Physical examination revealed a chronically ill white woman. The notable physical findings were a firm mass extending from beneath the angle of the left mandible forward to the left submental region. The right submaxillary area contained a firm mass the size of a baseball. The liver was palpable three fingers'-breadth below the costal margin and was smooth to palpation.

*Course.* A series of four daily injections of methyl-bis, begun March 4, 1947, resulted in marked relief from pain and a striking decrease in the size of the cervical lymph glands. However, only a slight decrease in the dysphagia and vomiting was noted.

The cervical glands remained small, relief from pain continued but marked dysphagia and vomiting returned a week after the course of methyl-bis was completed. Our supply of methyl-bis did not allow us to repeat the treatment. The patient died on April 13, 1947.

*Gross Autopsy.* No palpable cervical or axillary masses and no evidence of metastases to the lungs was noted. The liver showed two small tumor nodules and one nodule measuring 4 by 3 cm. A calculus, one centimeter in diameter, was impacted at the junction of the cystic and common bile ducts. Both kidneys showed diffuse neoplastic infiltrations.

*Microscopic Examination.* A section from a liver nodule was interpreted by Dr. R. J. Parsons as "lymphoblastoma, of large cell type, or a lymphosarcoma."

## SUMMARY

Two cases of Hodgkin's disease, treated with nitrogen mustard, methyl-bis ( $\beta$ -chloroethyl) amine hydrochloride, have responded favorably at a period when further roentgen-ray therapy was not considered advisable. The two living cases are pursuing gainful lives 10 months and eight months after initial methyl-bis therapy. The case which has been followed for 10 months is now receiving roentgen-ray therapy to an area of local recurrence.

Of the three cases of lymphosarcoma, treated after further roentgen-ray therapy was not deemed advisable, one is leading a useful home life eight months after initial therapy; one received marked subjective and objective relief but died in her sleep one month after the last course of therapy, and the third experienced considerable relief from pain, disappearance of peripheral lymphadenopathy, but no relief from dysphagia or vomiting. Autopsy revealed metastatic tumor nodules in the liver and kidneys.

## CONCLUSIONS

The position which methyl-bis ( $\beta$ -chloroethyl) amine hydrochloride will take in the treatment of Hodgkin's disease and lymphosarcoma is, as yet, undetermined. However, the fact that it is effective palliatively, in certain instances of these diseases, is apparent.

It is our plan at present to use roentgen-ray therapy to tolerance in both Hodgkin's disease and lymphosarcoma. The nitrogen mustards will be used when further radiation therapy is not available. As in our Case 1, local recurrences will be treated by x-radiation, if possible.

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## THE USE OF THE EXERCISE TEST IN THE DIAGNOSIS OF CORONARY INSUFFICIENCY \*

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THE differential diagnosis of precordial pain may present a difficult problem. It is for this reason that the electrocardiogram has recently gained such wide vogue. However, it is now apparent that a normal electrocardiogram does not necessarily exclude coronary disease and it is becoming clearer that other diseases can lead to electrocardiographic changes which may imitate coronary patterns. A need has developed for some tests to measure the adequacy of the coronary circulation. Two such tests are now being used. One is the anoxemia test, the other the exercise test. In both the judgment is based upon the electrocardiographic alteration. They have been widely used recently to confirm or to establish the diagnosis of coronary insufficiency. There is some controversy over which of the two gives more accurate information. The proponents of the anoxemia test claim a slight increase in accuracy of diagnosis,<sup>1,2</sup> but others have considered the two tests of equal value.<sup>3</sup> It appears to us that if any difference is present, it is probably slight.

On the other hand the question of availability and safety of the test must be considered. The equipment for the exercise test is simple compared to that needed for the anoxemia test. For the exercise test a metronome and a stairs of two steps are all that is needed. The anoxemia test requires tanks of oxygen and nitrogen, a mask, a mixing apparatus or an anesthesia machine. The percentage of significant unfavorable reactions is less with the exercise than with the anoxemia test. With the former, precordial pain, dyspnea and weakness are the main reactions noted and these can be quickly alleviated by stopping the exercise. With the anoxemia test, 100 per cent oxygen may be given for unfavorable reactions. However, with this test not only does precordial pain occur, but headache, cyanosis, anxiety, clonic tremors, marked bradycardia and shock have been reported and these latter reactions have occurred in controls as well as patients suspected of coronary insufficiency.<sup>4,5,6,7</sup> Pulmonary edema, cardiac arrest and even death<sup>8</sup> have occurred with the anoxemia test.

Confusion has arisen in regard to the exercise test because in the literature there has been considerable variability in the amount, type and rate of

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exercise as well as in the criteria employed to determine whether or not the test is abnormal. Master et al.<sup>9</sup> have emphasized the importance of standard amounts and rates of exercise and have established criteria for a "positive" test. These criteria are at variance with other reports in which a similar "2 step test" was also used but in which the amount and rate of exercise was not standardized for the age, weight and sex.<sup>1, 10, 11, 12, 13</sup>

In order to determine the efficacy of the 2 step test as an aid in the diagnosis of doubtful cases of coronary insufficiency we have performed 151 tests. We found, as did others, that while the majority of diagnoses of angina pectoris (coronary insufficiency) can be made from the history, there are some instances in which confirmation was needed. This is particularly true of patients in the younger age group. Often a history compatible with coronary insufficiency is discarded because of the age of the patient. The military services have emphasized that postmortem examinations reveal an unsuspected incidence of coronary disease in the younger individuals.<sup>14, 15</sup>

In the present study we have tried to evaluate the utility of the exercise test for our own guidance and to clarify the criteria by which a normal exercise test can be distinguished from an abnormal one. We were interested also in determining whether this test could be of value as a routine procedure in selected patients. We chose the exercise test, as already mentioned, because of its relative simplicity, the lack of necessity of specialized equipment, the relative freedom from untoward reactions and because it simulates most closely the type of exertion that the individual performs in his daily routine. In this study an attempt was made to use patients whose control electrocardiogram showed no definite evidence of coronary insufficiency. Both those suspected clinically of coronary disease and those who were considered to be normal were included in this series. The patients ranged in age from 15 to 84 years. Included were a number of instances of neurocirculatory asthenia or anxiety neurosis.

## METHOD

In each instance a careful cardiac history and physical examination was performed prior to the test. A clinical impression was made with particular reference to the presence or absence of angina pectoris. The Master "2 step test" was used according to the rules layed down by Master et al.<sup>9</sup> In practically all cases we attempted to perform a double test, i.e., twice the listed number of trips in twice the time. If precordial distress, marked dyspnea or weakness occurred, the test was concluded, noting the number of trips and the elapsed time. In all cases the three standard limb leads and three chest leads (CF<sub>2</sub>, CF<sub>4</sub> and CF<sub>5</sub>) \* were taken. The positions for the chest electrode were marked so that identical points were used throughout the test. A control tracing was taken in all cases prior to the test. After exercise, serial electrocardiograms were taken immediately, and in

\* We now use V<sub>2</sub>, V<sub>4</sub> and V<sub>6</sub>.

two and in 10 minutes. In many of the cases tracings were also taken six minutes after exercise. The limb leads were obtained within 20 seconds following completion of the exercise. The Sanborn (Instomatic) machine was employed to accelerate the shifting from one lead to another. All records were obtained with the patient reclining in bed. The reference point employed for S-T deviations was the isoelectric level (the level at the start of P). When tachycardia developed the P-Q segment was used as the level of reference.

## RESULTS

The results of exercise tests in normal individuals emphasize that certain electrocardiographic changes occur following exertion. These are similar to those occurring in patients with coronary insufficiency, but are less in extent. In our series of normal individuals the most significant changes occurred in the S-T segment. Slight fluctuations in T-wave amplitude occur in normal subjects and are not of diagnostic significance. In none of the normal subjects did an upright T-wave become indiscernible or inverted. However, in some normals with inverted T-waves in Lead III and in some who on occasion had an inverted T-wave in  $CF_2$ , the T-wave became upright following exercise.

As a result of our analysis, correlated with that in the literature, we have come to the conclusion that in certain cases more than isolated measurements of the S-T depression are necessary for the diagnosis of a positive test. When significant changes did occur they were present in two or more of the six leads. Significant S-T depression, we concluded, was 0.75 mm. or more in a limb lead and 1.50 mm. or more in a chest lead; significant T-wave changes include the appearance of indiscernible, diphasic or inverted T-waves in either Leads I, II,  $CF_4$  or  $CF_6$ . We found it valuable not only to look for these particular changes in S-T and T but to judge a test as positive or negative on the basis of the change in contour of the entire S-T-T complex. In our series no specific coronary pattern, of the type seen in acute myocardial infarction, developed following the exercise test, although such have been noted.<sup>16</sup> In one case, however, in which premature systoles developed, the premature systoles showed a coronary pattern in  $CF_2$  diagnostic of a positive test (figure 1). We consider that the development of frequent premature systoles, of intraventricular and A-V block<sup>3</sup> is usually indicative of a positive test.

Although most of our cases of suspected coronary insufficiency employed in the exercise test were patients with normal control electrocardiograms, it is probable that had we used less rigid criteria we would have obtained a greater percentage of positive tests. This is particularly true among the cases listed as doubtfully positive. Many of these latter showed major changes in one lead and minor changes in other leads. It is also likely that we would have obtained a greater percentage of positive tests had we accepted more patients with abnormal electrocardiograms.

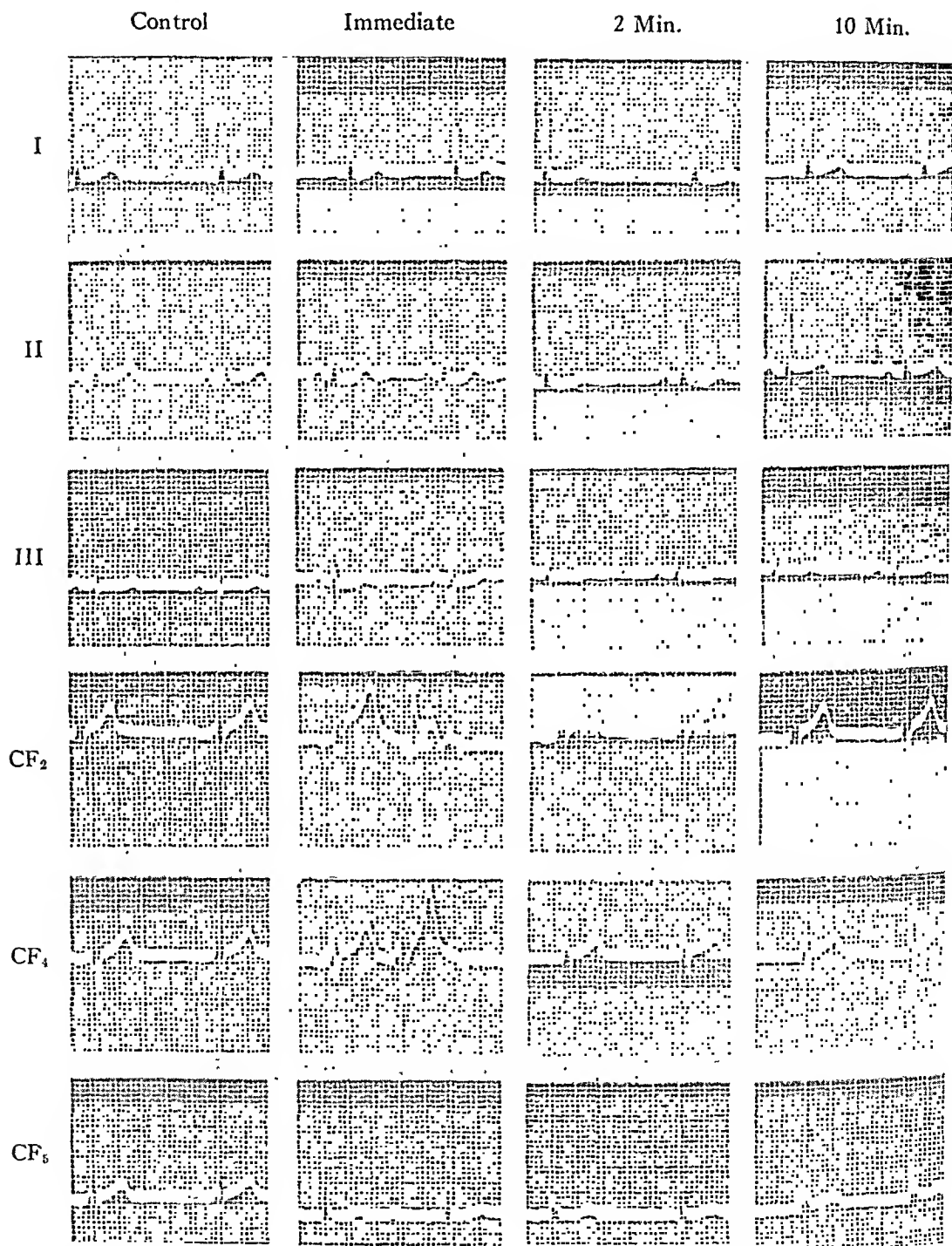


FIG. 1. A positive exercise test showing premature systoles with a coronary contour (in CF<sub>2</sub>). The two minute record shows the greatest flattening of the T-waves in the limb leads.

The results in our 151 patients are summarized in tables 1 and 2. Of the 151 patients, 43 gave a history compatible with coronary insufficiency; of these 43 cases, 22 had positive tests, four were doubtful and 17 were negative. In the remaining 108 patients the history was not suggestive of

TABLE I

Evaluation of Exercise Test on Basis of History, Symptoms during Test, Appearance of Control Electrocardiogram and Physical Findings of Heart Disease

		Exercise Test in Patients With						Exercise Test in Patients Who					
		History Suggestive of Angina Pectoris			History Negative for Angina Pectoris			Developed Precordial Distress, Dyspnea or Weakness During Test			Did Not Develop Precordial Distress, Dyspnea or Weakness During Test		
		Pos.*	Doubt.*	Neg.*	Pos.*	Doubt.*	Neg.*	Pos.*	Doubt.*	Neg.*	Pos.*	Doubt.*	Neg.*
Normal resting ECG	Without objective evidence of heart disease	13	0	5	2	2	76	11	7	7	4	2	74
	With heart disease	1	1	3	0	0	3	1	1	2	0	0	4
Abnormal resting ECG (no evidence of chronic coronary insufficiency)	Without objective evidence of heart disease	2	0	2	2	0	9	2	0	1	2	0	10
	With heart disease	6	3	7	3	1	10	7	2	4	2	2	13

108 controls—7 Pos., 3 Doubt.

43 non-controls—22 Pos., 4 Doubt.

\* Pos. indicates positive test, Doubt., a doubtful test, Neg., a negative test.

TABLE II

Correlation of Symptoms Occurring during Test with Electrocardiographic Test and Clinical Evaluation

	History of Coronary Insufficiency	No History of Coronary Insufficiency
Test positive, symptoms during test positive	18	3
Test negative, symptoms during test negative	11	90
Test positive, symptoms during test negative	4	4
Test negative, symptoms during test positive	6	8
Test doubtful, symptoms during test positive	3	0
Test doubtful, symptoms during test negative	1	3
Totals	43	108

coronary insufficiency; 83 of these 108 cases had normal electrocardiograms and in 79 of them the test was negative. However, in this group there were two positive and two doubtful tests. One of the positive tests was in a 37 year old woman who had atypical precordial pain and the other in a 52 year old man who had three episodes of "gnawing chest pain" but otherwise a negative history. These two cases may very well have been classified as clinically suspected coronary insufficiency. Of the 108 cases whose history was not suggestive of coronary insufficiency, 25 had an abnormal control electrocardiogram. In 19 of these the test was negative, in one it was doubtful and in five it was positive. The positive tests were obtained on:

1. A 63 years old diabetic with exertional dyspnea.
2. A 45 year old physician with intraventricular block but no symptoms and signs of heart disease.
3. A 40 year old woman with marked hypertension.
4. A 40 year old man who had recurring premature systoles.
5. A 24 year old woman with a Lutembacher syndrome.

Thus, it is possible that at least in the first four cases the suspicion of coronary insufficiency may be entertained.

It is worthy of note that the proportions of positive tests in the control and suspected coronary insufficiency groups is approximately the same as that reported by Master<sup>9</sup> using a similar exercise test, and by Levy<sup>4</sup> and Biorck<sup>1</sup> with anoxemia tests.

It is interesting to note that 38 of the 151 patients developed either chest pain, moderate dyspnea, weakness or dizziness during the test. In all instances the symptoms were minor and in every instance cessation of exercise resulted in the disappearance of the symptoms. In table 2 the results of the exercise test are correlated with the occurrence of these symptoms. It will be noted that of 21 patients, in whom a positive test was obtained at the same time that symptoms developed, 18 had a history of coronary insufficiency. On the other hand, of the 101 patients who had a negative test and did not develop symptoms, 90 had a history that was not compatible with coronary insufficiency. It would thus appear that the occurrence of symptoms tends to fortify the estimate based on the electrocardiographic alterations.

## DISCUSSION

Electrocardiographic changes following exercise can not be ascribed exclusively to the development of a relatively inadequate coronary flow. Other factors set up by exercise may play a significant rôle. It is notorious that a number of influences exclusive of anoxemia and ischemia lead to depression of the S-T segment and flattening, and even inversion of the T-wave. Thus, Wendkos<sup>17</sup> found such S-T and T-wave changes occurring in normal individuals following change in position. Increased activity of the sympathetic nervous system can produce such changes and patients with neurocirculatory asthenia and anxiety are prone to exhibit them. These patients will often present symptoms referable to the cardiovascular system. Walser<sup>18</sup> showed that mild exertion lowered the T-wave in normal subjects and that strenuous exercise, while at first increasing the height of the T-wave, later diminished it. Furthermore he found that sympathomimetic drugs exaggerated this response while sympatholytic drugs lessened this effect. Chapuis<sup>19</sup> suggested that sympatholytic drugs might be used to distinguish the electrocardiographic changes produced by exercise on the basis of an underlying organic coronary disease from those due to reflex augmentation of adrenergic influences. He employed dihydroergotamine intravenously in the two groups of patients prior to the induction of anoxemia. Wendkos<sup>20</sup> also has used such drugs to differentiate sympathogenic distortions of the T-wave from those due to intrinsic cardiac disease.

Two other accompaniments of exercise are known to influence the electrocardiogram. These are tachycardia and hyperventilation. The S-T depression caused by tachycardia is well known. To a large extent this is due to the increased size of the auricular T-wave ( $T_A$ ) which leads to a simul-

taneous depression of the P-Q segment. To exclude this factor we have used the level of the P-Q segment as a reference point whenever a tachycardia of moderate degree or more developed. Hyperventilation decreases the CO<sub>2</sub> content of the blood and hypocapnia has been shown to lead to S-T depression and T-wave inversion.<sup>21, 22</sup>

We recognize that these factors as well as the development of relative coronary insufficiency play a rôle in the electrocardiographic criteria used in judging whether an exercise test is positive or negative. The judgment of the test is empirical and is based on a comparison of the electrocardiographic changes in known cases of coronary insufficiency with those in known normal subjects. This is the method employed in our study. We have felt that it is essential to include, besides the positive and negative groups, a class of doubtfully positive tests. We have tried to eliminate other variables such as previous fatigue, recent meals<sup>23, 24</sup> and marked changes in room temperature. Our criteria for the test demand as great or

TABLE III  
Criteria Used in Exercise Test

Author	S-T Depression or Elevation	T-Wave Changes	Other Changes
Twiss and Sokolow <sup>10</sup>	1.0 mm. or more in I 1.5 mm. or more in II 1.5 mm. or more in III 2.0 mm. or more in IV	Change from upright to a diphasic or inverted T <sub>1</sub> , T <sub>2</sub> or T <sub>4</sub> .	
Levan <sup>*12</sup>	0.75 mm. or more depression in any lead	Change from upright to isoelectric or negative T <sub>1</sub> , T <sub>2</sub> or T in chest leads. Change from isoelectric to a well-developed T-wave in I and II.	Also consideration of dwarfing of the QRS amplitude.
Maser and Reisinger <sup>11</sup>	0.75 mm. or more in I 1.5 mm. or more in II 0.75 mm. or more in III 1.75 mm. or more in CF <sub>4</sub>	Inversion of T-waves in Leads I, II or CF <sub>4</sub> .	Low voltage of T-waves in all limb leads.
Master <sup>*3</sup>	0.5 mm. or more in any lead	Change from upright to isoelectric or inverted T. Change from negative to positive T-wave.	Premature beats or significant arrhythmias, widening of QRS, large Q waves, prolongation of P-R interval.
Biorck <sup>1</sup>	Total of 2.0 mm. or more in limb leads 1.5 mm. or more in any lead	Inversion of T <sub>1</sub> , or T <sub>2</sub> .	Diphasic T <sub>1</sub> with S-T depression of 1.0 mm. or more.
Our present report	0.75 mm. or more in a limb lead 1.50 mm. or more in a chest lead	Change from upright to isoelectric or inverted T. Change from negative to positive T (in Leads I, II, CF <sub>2</sub> and CF <sub>4</sub> ).	Occurrence of coronary pattern. Significant premature systoles, intraventricular or auriculo-ventricular block.

\* Used isoelectric point (beginning of P-wave) as the reference point for depression and elevation of S-T segment.

greater change from the normal than that employed by any other group using a standardized technic. This is shown in table 3 which compares the criteria used by various investigators.

In the course of this study it was found that the maximum changes in S-T deviation and T-wave amplitude occurred in some instances several

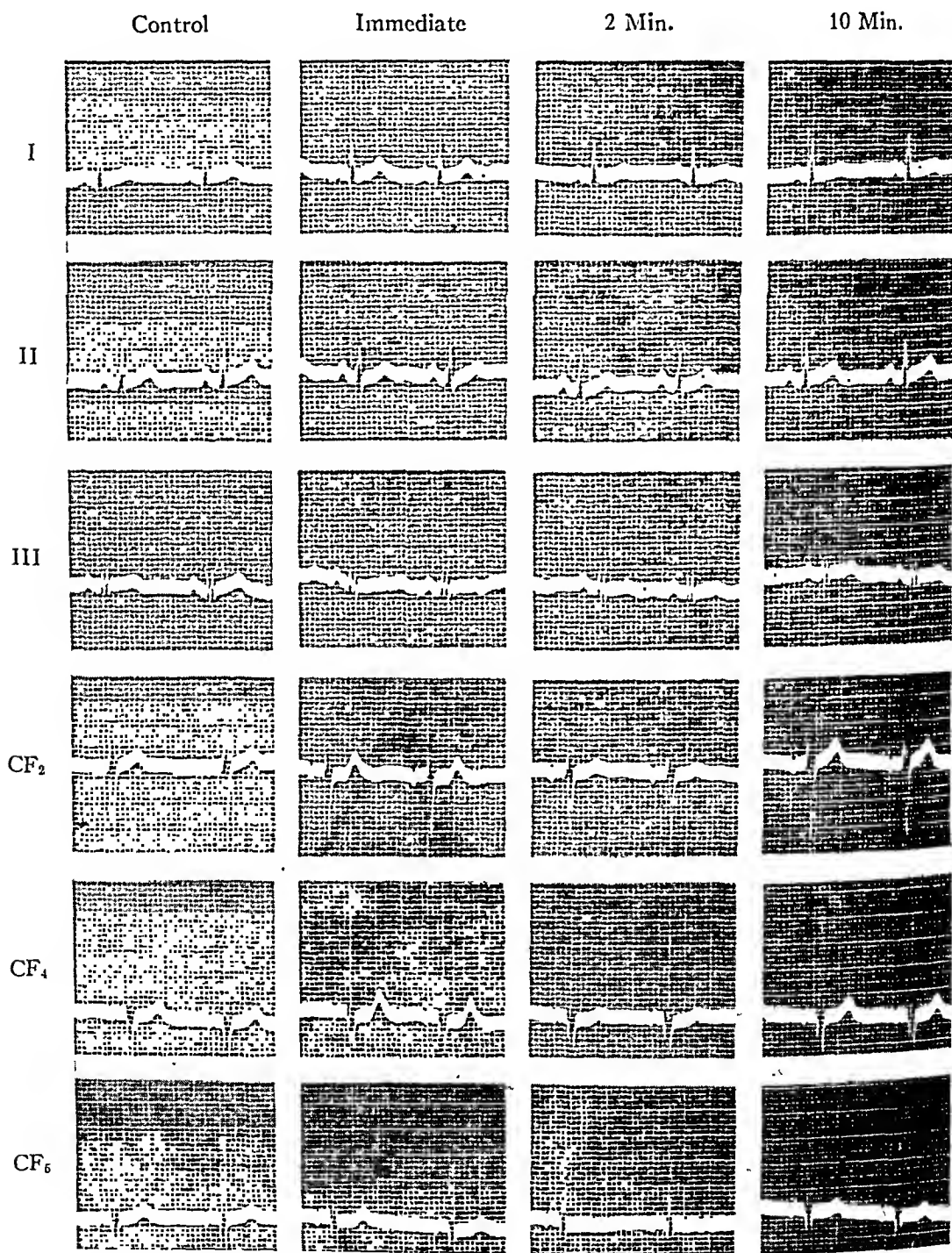


FIG. 2. A positive exercise test in which the maximal changes appear in the record taken two minutes after completion of exercise. Note the marked flattening of the T-waves in the chest leads of the two minute electrocardiogram.



minutes after completion of the test. In two cases, records taken immediately following exercise would have been judged as a negative test while records taken two to six minutes following the exercise showed a positive test (figure 2). It is possible that such "delayed positive" tests might be missed with the anoxemia test since patients may be allowed to breathe 100 per cent oxygen immediately following the period of anoxemia.

It would appear from our experience that the exercise test, when performed by a well-qualified physician with due regard for the safety of the patient, has a definite place in the differential diagnosis of coronary insufficiency. While a negative test does not exclude coronary insufficiency, a positive one fortifies this diagnosis. If liberal standards are employed, false positive tests will be rare. This is not disturbing inasmuch as the exercise test is not the final criterion, but one of a series of evaluations which should lead the clinician to his final judgment. It is obvious that further experience with larger numbers of cases should improve the criteria to be employed in judging the results of the test and thereby should make it more useful in the future. There is no point in using the test when the clinical picture is definite or the resting electrocardiogram shows a coronary contour. There is no point in using the test when there is no suspicion of coronary disease. The real value of the test lies in cases in which the diagnosis is in doubt. However, the test should be employed in known cases of coronary disease and in known normals so that the number of cases from which to build standards can be multiplied. Even with this test great caution should be used when the differential diagnosis is between coronary disease on the one hand and neurocirculatory asthenia and anxiety states on the other.

### SUMMARY

1. A standardized exercise test using the Master 2 step stairs was employed in 151 patients, 108 of whom had no history or findings suggestive of coronary insufficiency and 43 of whom had a definite or questionable history or findings of coronary insufficiency. With few exceptions these cases had control electrocardiograms within normal limits. In practically all cases we attempted to perform a double test, i.e., twice the listed number of trips in twice the time set by Master for the given age, sex and weight of the patient.

2. A test was considered positive when there was a significant S-T depression in two or more leads, viz., 0.75 mm. or more in a limb lead and 1.50 mm. or more in a chest lead. A test was also considered positive when the T-wave in Leads I, II, CF<sub>4</sub> or CF<sub>5</sub> became indiscernible, diphasic or inverted. Frequent premature systoles, intraventricular block, A-V block, and the development of a pattern suggestive of myocardial infarction were also considered evidence of a positive test.

3. No diagnostic significance was attached to the development only of an inverted T-wave in Lead III or of T in CF<sub>2</sub> becoming upright following exercise.

4. The correlation of positive tests in the various groups coincided with that reported in previous standardized exercise and anoxemia tests. It was found necessary to include a grouping labelled doubtful positive tests.

5. The development of precordial pain, dyspnea, weakness or dizziness occurred in 38 patients. This was considered supportive evidence of a positive test. When such symptoms occurred the exercise was stopped. In no instance were these symptoms striking.

6. Although a positive test is of diagnostic value (we have not encountered a false positive test in this series), a negative test does not exclude coronary disease.

7. Occasionally the record immediately after exercise is negative or inconclusive only to become positive after a latent period of two to six minutes. It is therefore essential that records be taken at least once during this period.

8. The mechanisms for the development of the electrocardiographic changes are discussed.

9. It is concluded that when properly executed the exercise test is a useful adjuvant in the differential diagnosis of coronary insufficiency.

We are indebted to the house officers of this department for assistance with the test and to physicians of the hospital staff for permitting us to study their patients.

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# THE EFFECT OF CARONAMIDE ON THE BLOOD CONCENTRATION OF PENICILLIN FOLLOWING ORAL AND INTRAMUSCULAR ADMINISTRATION OF PENICILLIN \*

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ONE of the greatest problems in the clinical use of penicillin has been the maintenance of adequate plasma concentrations in spite of the rapid rate at which the antibiotic is excreted by the kidneys. Recently Sprague and his associates<sup>1</sup> have developed a drug, caronamide (4' carboxyphenyl-methanesulfonanilide) which inhibits the renal excretion of penicillin. Beyer<sup>2,3</sup> has postulated that caronamide suppresses penicillin excretion by blocking the specific enzyme system responsible for penicillin transport through the tubular cells. Since it has been demonstrated<sup>2,4</sup> that of the penicillin excreted about 20 per cent passes into the urine through the glomeruli and 80 per cent through the tubules, the concurrent administration of caronamide and penicillin should theoretically give higher and more prolonged plasma concentrations of penicillin.

Information concerning the chemistry,<sup>5</sup> physiology,<sup>5</sup> pharmacology,<sup>6</sup> toxicology,<sup>7</sup> and early clinical investigation<sup>8</sup> of caronamide has appeared in recent literature. It is the purpose of this paper to present the results we have obtained from the study of the effect of caronamide upon the serum penicillin concentrations in a group of patients treated at the Gallinger Municipal Hospital with varying doses of penicillin and caronamide.

## METHOD OF STUDY

Patients who were receiving penicillin either orally or parenterally were selected for the study, provided they showed no evidence of impaired renal function. In order to evaluate the effect of caronamide, the concentrations of penicillin in the blood were determined following the administration of penicillin alone and then with the same dose of penicillin plus caronamide. Each patient served as his own control for the studies. In order to simulate clinical conditions as nearly as possible, the patients were given penicillin and caronamide for 12 hours or more before blood for penicillin determinations was obtained. The "caronamide bloods" were drawn 24 hours after the "control bloods" at the corresponding hourly intervals in the same patients.

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Penicillin concentrations in the sera were then assayed using a modification of the Rammelkamp method.<sup>9</sup>\*

The results have been tabulated according to a hypothetical fraction, the numerator of which represents the hourly caronamide-penicillin levels and the denominator the hourly control-penicillin levels. The fold increase, or caronamide effect for each of the hours was determined by dividing the caronamide levels by the control levels. An example of this method of tabulation is presented:

	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.
$\frac{\text{caronamide level}}{\text{control level}}$	$\frac{1.25}{.156}$	$\frac{.312}{.078}$	$\frac{.156}{.039}$	$\frac{.078}{.039}$
fold increase = $\frac{\text{caronamide level}}{\text{control level}}$ =	8	4	4	2

In order to ascertain the toxicity of caronamide before beginning the study, four patients were given 24 gm. (4 gm. every four hours) per day for seven days. During this period, frequent urinalyses, hemograms, and blood urea nitrogen determinations were obtained. The patients were also observed carefully for any other evidences of toxicity. In an effort to determine the sensitizing effect of caronamide, a second course of the drug was administered to a group of 22 patients seven to fourteen days following an original course of five days, and they were observed particularly for allergic manifestations of drug fever, rash, and conjunctivitis.

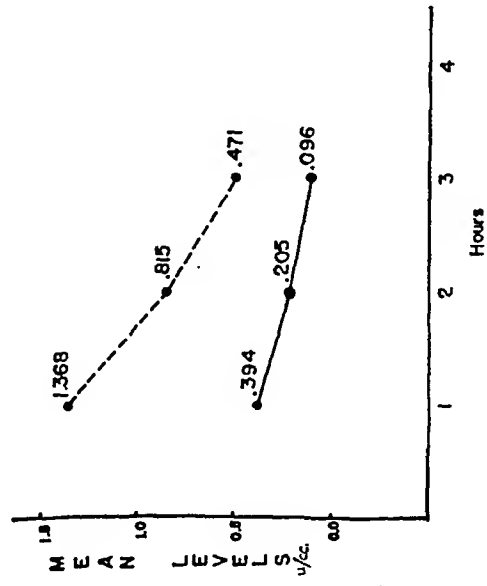
## RESULTS

We have administered oral caronamide to 106 patients using varying doses of caronamide and penicillin. Forty of these patients received penicillin by intermittent intramuscular injections. The remaining 66 patients received penicillin by the oral route. The dosage schedules of penicillin most commonly employed were 30,000 units intramuscularly every three hours (26 patients) and 100,000 units every four hours orally (59 patients). These two groups of patients will be referred to hereafter as the *selected intramuscular* or *selected oral series* since statistical evaluation of our results will be concerned chiefly with these groups. When they are considered together, they will be referred to as the *total selected series*.

The mean penicillin serum concentrations and fold increases were calculated for each of the hourly intervals. These mean concentrations for all the patients studied in the *selected series* are shown in figure 1a and for the *selected intramuscular and oral series* in figures 1b and 1c, respectively. It is obvious that caronamide has the ability to increase the concentrations of penicillin in the serum. The statistical significance of the differences between the mean caronamide levels and the mean control penicillin levels was determined according to the method described by Hill.<sup>10</sup> The differences

\* A serial two-fold dilution method comparing the inhibition of a test organism by known and unknown amounts of penicillin.

Effect of the oral administration of coronamide on the concentrations of penicillin in the blood following oral and intramuscular administration. (Total selected series.)

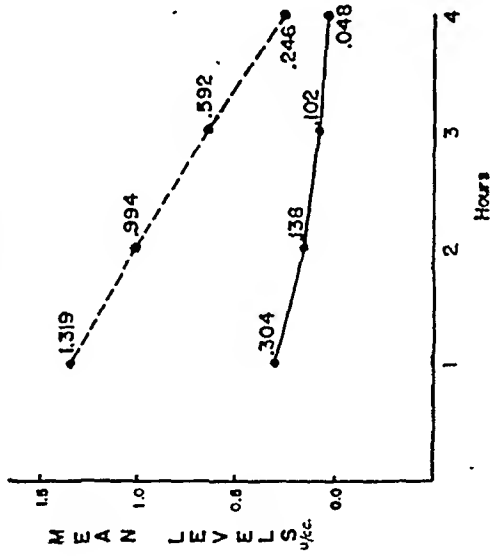


HOUR	t	°F	F.I.
1	5.8	168	3.9
2	3.6	168	3.9
3	2.6	171	4.9

— Control penicillin curve  
 --- Coronamide-penicillin curve  
 t = Value for difference between the means

Fig. 1 a.

Effect of the oral administration of coronamide on the concentrations of penicillin in the blood following oral administration of 100,000 units every four hours. (Selected oral series)

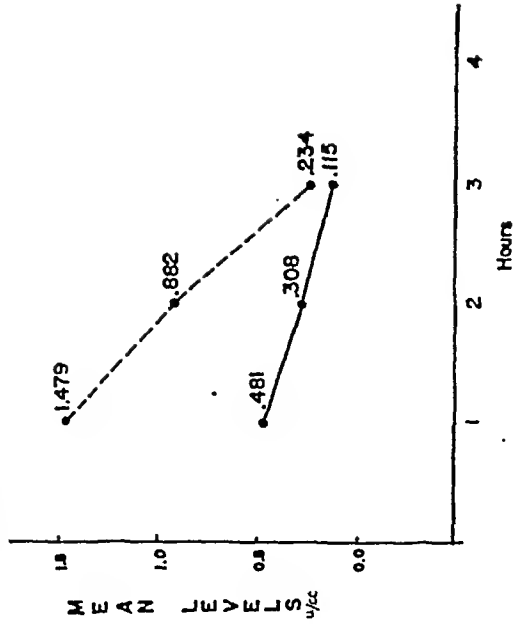


HOUR	t	°F	F.I.
1	4.8	116	4.3
2	4.8	116	7.2
3	3.5	116	5.8
4	1.2*	116	5.1

°F = Total degrees of freedom.  
 F.I. = Fold Increase  
 \* = Not statistically significant

Fig. 1 b.

Effect of oral administration of coronamide on the concentration of penicillin in the blood following intramuscular administration of 20,000u. every 3 hours. (Selected intramuscular series)



HOUR	t	°F	F.I.
1	4.0	50	3.0
2	4.0	50	2.8
3	1.1*	53	2.0

Fig. 1 c.

between the means are highly significant for the *total selected series* and for the *selected intramuscular and oral series* respectively at each of the hours except at the third hour for the *selected intramuscular series* and at the fourth hour for the *selected oral series*.

The average fold increase (caronamide effect) for the *total selected series* is 4.3 with a range from zero to 128 in individual patients. In general, patients not included in the *selected series* had fold increases similar to those in the selected group. Furthermore it can be seen from the figures that the fold increases were fairly uniform for each of the hours. The highest caronamide-penicillin levels, on the other hand, were noted at the first hour and diminished gradually thereafter. The rate of decrement seemed to be fairly constant as indicated by the almost straight line of the caronamide-penicillin curves.

The effect of different dosage schedules of caronamide on a constant dose of penicillin is tabulated in tables 1 and 2. There are no striking differences in the caronamide effect with the various doses of caronamide employed in the series. The mean penicillin concentrations obtained with 3 gm. and 4 gm. of caronamide given every three or four hours respectively, are greater than those obtained with the lower dosage regimens, but the standard deviation from the means is so great that the differences are not statistically significant. That these larger doses have a greater effect than the smaller amounts is suggested, but proof would depend on obtaining similar results in a larger series of patients. The results in the patients who received 2 gm. every two hours do not differ significantly from those in the patients who were given 4 gm. every four hours, but in a larger series the higher means for the latter dosage-schedule might have statistical significance.

When the mean caronamide-penicillin levels obtained with each component series of the *selected intramuscular group* are compared with the mean penicillin levels for the *selected control group*, the differences between the means are significant only at the first hour. The differences between the means for the corresponding figures in the *selected oral series*, on the other hand, are significant at all the hours. In general, the results in the *selected intramuscular series* are not as consistent as those in the *selected oral series*. This variability can be explained by the fact that the former series is smaller than the latter.

Although statistical analysis of the *total selected series* shows significant effect of caronamide for each of the hours, we have observed frequent variation in the response of individual patients. Table 3 shows this variation in response. Approximately 50 per cent of patients failed to show an increase at the fourth hour and did not maintain a serum concentration of penicillin of at least .078 unit per c.c. at this time. Twenty-three per cent of patients had no detectable increase at any one of the hours; 21 per cent had none at two of the hours; 11 per cent had none at three of the hours; and 5 per cent had none at four of the hours. Eight per cent had no response at any of

the hours tested. Patients showing no increase at one or two of the hours for the most part were those who showed no response during the third and/or fourth hours. Forty-nine per cent of patients in the total series maintained levels of .078 unit per c.c. or higher of penicillin continuously for all hours after receiving caronamide as compared with 15 per cent in the

TABLE I  
Caronamide Effect for Selected Intramuscular Series 30,000 Units  
Penicillin Every Three Hours with Varying  
Doses of Caronamide

Doses of Caronamide	Number of Cases		Versus Own Control			Versus Group Control		
			1 Hr.	2 Hrs.	3 Hrs.	1 Hr.	2 Hrs.	3 Hrs.
2 gm. every four hours	5	CM	1.109	.398	.242	1.109	.398	.285
		CT	.249	.046	.019	.481	.308	.115
		t	2.9	2.4	1.3*	2.3	0.3*	1.5*
		°F	8	8	8	29	29	29
		FI	4.4	8.6	12.7	2.3	1.3	2.5
2 gm. every three hours	7	CM	2.44	.535	.290	2.44	.535	.290
		CT	.535	.577	.150	.481	.308	.115
		t	1.9*	—	—	3.8	0.7*	1.2*
		°F	13	—	13	31	31	31
		FI	4.5	—	1.8	5.05	1.7	2.5
2.5 gm. every three hours	7	CM	.384	.147	.055	.439	.147	.055
		CT	.304	.097	.025	.481	.308	.115
		t	0.3*	0.3*	0.5*	—	—	—
		°F	12	12	12	—	—	—
		FI	1.2	1.5	2.2	—	—	—
3 gm. every three hours	7	CM	1.540	.585	.446	1.540	.585	.446
		CT	.753	.441	.111	.481	.308	.115
		t	1.5*	0.4*	1.5*	3.6	0.8*	2.1
		°F	12	12	12	31	31	31
		FI	2.0	1.3	4.0	3.2	1.9	3.8

CM = mean level for caronamide.

CT = mean level for control.

t = t value for the difference between means.

\* = t value not statistically significant.

°F = degrees of freedom.

FI = fold increase =  $\frac{\text{mean caronamide level}}{\text{mean control level}}$ .



TABLE II  
Caronamide Effect for Selected Oral Series 100,000 Units  
Penicillin Every Four Hours

Doses of Caronamide	Number of Cases		Versus Own Control				Versus Group Control			
			1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.
2 gm. every four hours	14	CM	1.451	.741	.350	.171	1.451	.741	.350	.171
		CT	.118	.082	.042	.019	.304	.138	.102	.048
		t	2.3	2.1	2.1	2.0	3.5	3.8	2.8	2.3
		°F	26	26	26	26	71	71	71	71
		FI	12.3	9.0	8.3	9.0	4.8	5.4	3.4	3.6
3 gm. every four hours	17	CM	.811	.992	.674	.223	.811	.992	.674	.223
		CT	.468	.232	.150	.047	.304	.138	.102	.048
		t	1.1*	2.4	1.6*	1.5*	3.05	3.6	2.6	2.4
		°F	32	32	32	32	74	74	74	74
		FI	1.7	4.3	4.5	4.7	2.7	7.2	6.6	4.6
4 gm. every four hours	13	CM	1.900	1.634	.779	.394	1.900	1.634	.779	.394
		CT	.319	.142	.139	.089	.304	.138	.102	.048
		t	3.9	3.8	3.4	2.0	6.8	7.6	6.8	4.6
		°F	24	24	24	24	70	70	70	70
		FI	5.9	11.5	5.6	4.4	6.2	11.8	7.6	8.2
2 gm. every two hours	15	CM	1.266	.681	.565	.238	1.266	.681	.565	.238
		CT	.126	.104	.072	.040	.304	.138	.102	.048
		t	3.1	3.4	2.7	3.1	4.2	4.9	4.7	4.1
		°F	28	28	28	28	72	72	72	72
		FI	1.0	6.5	7.9	5.9	4.2	4.9	5.5	5.0

CM = mean level for caronamide.

CT = mean level for control.

t = t value for the difference between means.

\* = t value not statistically significant.

°F = degrees of freedom.

FI = fold increase =  $\frac{\text{mean caronamide level}}{\text{mean control level}}$ .

control group. Whereas 8 per cent of those receiving caronamide did not maintain a level of .078 unit per c.c. for any of the hours, the incidence in the control group of those who did not maintain such a serum concentration was 26 per cent. These differences are highly significant when tested by the chi square method and indicate a definite advantage of the use of caronamide with penicillin over the use of penicillin alone.

TABLE III  
Per cent of Patients Showing Caronamide Effect

	Number of Cases According to Hours	Per Cent of Patients with No Fold Increase at				Per Cent of Patients with No Fold Increase at					
		1st Hr.	2nd Hr.	3rd Hr.	4th Hr.	One of the Hours	Two of the Hours	Three of the Hours	Four of the Hours	Any of the Hours	
Total series	1-106 2-106 3-102 4- 67	25	22	35	49	23	21	11	5	8	
Total intramuscular series	1- 40 2- 40 3- 36 4- 6	35	30	50	50	25	30	8	17	10	
Total oral series	1- 66 2- 66 3- 66 4- 61	18	17	27	49	21	17	14	3	6	
	Number of Cases According to Hours	Per Cent of Patients without a Level of .078 or Higher at				Per Cent of Patients with a Level of .078 or Higher Continuously for					
		1st Hr.	2nd Hr.	3rd Hr.	4th Hr.	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	All Hours	None of the Hours
Total series	CT 1-106 2-106	26	59	77	88	39	16	12	11	15	26
	CM 3-102 4- 67	8	16	36	52	8	25	28	44	49	8
Total intramuscular series	CT 1- 40 2- 40	8	58	78	33	50	25	14	33	23	8
	CM 3- 36 4- 6	10	27	53	50	18	32	36	50	48	10
Total oral series	CT 1- 66 2- 66	38	59	76	90	32	11	11	8	11	38
	CM 3- 66 4- 61	8	9	27	52	3	20	24	49	50	8

CT—control.

CM—caronamide. All percentage figures have been rounded.

The figures for the selected oral and intramuscular series are essentially the same as those for the total oral and total intramuscular groups respectively, and are thus excluded from the table.

Evidence of acute toxicity to caronamide was not observed, save for 10 instances of nausea and/or vomiting. This complication in most instances, however, may be attributable to mechanical irritation of the gastrointestinal tract caused by the large 0.5 gm. caronamide tablets when doses of 3 to 4 gm. every three to four hours were employed. None of the 22 patients who received second courses of the drug had evidence of fever, rash,

or conjunctivitis. We have not studied chronic toxicity of caronamide in a sufficiently large group of patients to make any deductions. One patient, however, received 12 gm. per day for 56 days without ill effect.

Twelve patients in our series were over the age of sixty. These patients showed no difference in response to caronamide administration than did other patients who were younger than 60 years.

Other investigators<sup>11</sup> have noted that caronamide will prolong the concentrations of penicillin in the blood for from four to eight hours following administration of 100,000 units intramuscularly. We became interested in the possibility of maintaining the concentrations of penicillin in the blood following the administration of a large single dose of penicillin plus caronamide at regular intervals thereafter. Consequently, one million units of crystalline penicillin G was given intramuscularly to 12 patients in a single injection plus 4 gm. of caronamide which was continued at four hour intervals thereafter for 24 hours. Caronamide prolonged the concentrations of penicillin in the blood (beyond the twelfth hour) in only one patient (until the sixteenth hour).

#### COMMENT

Oral caronamide is definitely efficacious in raising serum concentrations of penicillin. Furthermore, its effect is independent of the route of administration of penicillin. Seeler and associates<sup>11</sup> and Strauss and co-workers<sup>12</sup> have reported similar experiences. Since concentrations of penicillin in the blood can usually be raised to desired levels with greater facility following parenteral rather than oral administrations, we believe that caronamide will be used to best clinical advantage in conjunction with oral penicillin. It is well established that serum concentration following oral administration shows tremendous variation due to differences in the ability of patients to absorb the antibiotic. Our results indicate that 2 to 4 gm. of caronamide when administered with 100,000 units of oral penicillin give adequate serum concentrations for three to four hours in the majority of patients, a great improvement over the use of penicillin alone. It should be borne in mind, nevertheless, that approximately 8 per cent of patients receiving caronamide show no effect (either by measurement of fold increase or by ability to maintain a level of .078 unit per c.c. of penicillin continuously for all of the hours) regardless of the route of administration of penicillin.

In general the recommended dose is 4 gm. given every four hours. Seeler and his associates<sup>11</sup> reported that in patients over the age of 60 the effect of caronamide can be obtained with one-half the dose employed in younger individuals. We noted no such differences in the 12 patients over the age of 60 in our series of 106 patients.

Others as well as we have not observed any acute or chronic toxic effect in patients other than nausea and vomiting. Crossen<sup>13, 14</sup> has commented that in view of the chemistry of the compound and extensive experience during the past 12 years with sulfonamides which are related chemically to

caronamide, widespread use of caronamide will undoubtedly reveal some type of sensitivity or toxic manifestations. A suspension of caronamide\* has recently appeared which contains 3 gm. of the drug per tablespoon. This preparation should decrease the incidence of nausea and vomiting if, as we believe, they are caused from mechanical irritation of the gastrointestinal tract by the bulky caronamide tablets.

Since experience with the use of caronamide has been brief, many problems concerning the use of caronamide with penicillin remain for future investigation. We are reporting the results of our study on one phase of the problem, namely the effect of caronamide in increasing the height of the concentration of penicillin in the blood following intramuscular and oral administration. The questions of chronic toxicity and the optimal penicillin-caronamide dosage and time relationship are still unsettled. The effect of caronamide on the oral administration of penicillin is obvious. When penicillin is administered parenterally, it may be more economical to increase the dose of penicillin rather than give caronamide if higher and more sustained concentrations of penicillin are desired.

#### SUMMARY AND CONCLUSIONS

1. Caronamide was administered orally to 106 patients in an effort to determine its ability to increase the concentrations of penicillin in the serum.

2. Caronamide increased the height of the serum penicillin concentrations for at least one of the hourly intervals tested in 92 per cent of the patients.

3. The average increase in serum penicillin concentrations attained with the use of penicillin plus caronamide over that obtained with the use of penicillin alone was approximately fourfold, regardless of the route of administration of penicillin.

4. The acute toxicity of caronamide is negligible. The order of chronic toxicity is as yet undetermined.

5. A recommended dose of caronamide is 4 gm. given every four hours.

6. Caronamide is used to best advantage clinically in combination with oral penicillin.

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# CASE REPORTS

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## HEMOLYTIC ANEMIA ASSOCIATED WITH ATYPICAL HEMAGGLUTININS \*

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THERE are in the literature scattered reports of cases of hemolytic anemia with demonstrable atypical iso- and autohemagglutinins. Reisner and Kalkstein<sup>1</sup> in 1942 found in the literature 54 case histories of patients with anemia whose bloods showed autohemagglutination. They reported an additional case of hemolytic anemia with autohemagglutinins. Wiener,<sup>2</sup> Baar,<sup>3</sup> Kracke and Hoffman,<sup>4</sup> Evans,<sup>5</sup> and Rennert and McShane,<sup>6</sup> have reported cases of hemolytic anemia associated with autohemagglutinins active at 37° C.

Callender and Paykoc<sup>7</sup> recently studied the sera of 100 patients who had been transfused with a total of 958 pints of whole blood. Two patients with hemolytic anemia, one of whom had an associated lymphatic leukemia, showed autohemagglutination at 37° C., room temperature, and 4° C. The sera did not agglutinate any other than the patient's own cells at 37° C.

Boorman, et al.<sup>8</sup> observed the development of atypical isohemagglutinins active at 37° C. following transfusion of whole blood to three patients. Two other cases, following transfusions, developed atypical cold isohemagglutinins, and one other developed a cold autohemagglutinin.

This communication is concerned with observations made in a fatal case of hemolytic anemia characterized by the presence of a high concentration of a pan-hemagglutinin effective only at low temperatures (cold hemagglutinin) as well as a separate hemagglutinin active at body temperature against the patient's cells and 63 per cent of red blood cells of Groups O and A.

### MATERIALS AND METHODS

The patient's blood (type A<sub>1</sub> N Rh<sub>1</sub>) was collected in a warm syringe and placed in serological tubes at room temperature until clot formation occurred. The specimens were then centrifuged and the supernatant serum drawn off and placed in the icebox until tested. More than the usual number of saline washings of the red cells were necessary, as they still tended to agglutinate following three such procedures. This tendency disappeared after a total of 12 saline washings. Therefore, the cells were washed 12 times in saline initially warmed to 37° C. and centrifuged in warmed centrifuge cups. Titrations for autohemagglutinins were done by mixing a 2 per cent saline suspension of the patient's own cells with equal aliquots of serial dilutions of the patient's serum.

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Titration for isohemagglutination were determined by utilizing 2 per cent saline suspensions of A<sub>1</sub> Rh<sub>1</sub> erythrocytes (washed three times at room temperature with physiological saline) in equal portions of serial dilutions of the patient's serum. The serum was titered serially for auto- and isohemagglutination at 8° C. and 37° C. shortly after withdrawal from the patient. All tubes were incubated at the desired temperature for one hour. The titrations for cold agglutinins were then placed in the refrigerator for an additional 12 to 18 hour period.

The experimental criteria of Stats and Wasserman<sup>9</sup> for cold hemagglutination were carried out. These included (a) agglutination of homologous erythrocytes at low temperature with reversal of the reaction upon increasing the temperature, (b) agglutination of the resuspended cell serum mixture upon chilling, (c) exhaustion of the agglutinins in the serum by absorption with erythrocytes at low temperature, (d) release of the agglutinins from the cold agglutinated erythrocytes by raising the temperature to approximately 37° C. Hemagglutinin titers in table 1 are expressed in units, each unit being the reciprocal of the dilution factor.

Specificity of the patient's warm agglutinating antibodies was determined by the use of a series of 2 per cent saline suspensions of washed erythrocytes which had been typed for A, O, M, N and Rh and its subtypes by the use of the corresponding antisera. Equal portions of the cells and serum suspensions were incubated for one hour at 37° C., centrifuged at moderate speed and read microscopically (table 2).

Isolation of the cold hemagglutinin (panagglutinin) from the warm hemagglutinin was accomplished by the following adsorption technics: saline suspensions of homologous type red blood cells which, on previous testing, had shown no agglutination at 37° C. with this serum were centrifuged and the supernatant saline withdrawn. Equal portions of the packed red cells and the patient's serum were placed in serological tubes and incubated with intermittent agitation at 8° C. and at 37° C. for a period of two hours. (Table 3). The 37° C. serum cell suspension was centrifuged in warmed cups and the supernatant withdrawn (Sample A). The 8° C. serum cell suspension was then centrifuged in ice-filled cups and the serum removed (Sample B). The supernatant serums from both aliquots were then titered for cold hemagglutinins, and also the supernatant serum from the 8° C. aliquot (Sample C) was titered for warm hemagglutinins. Saline suspensions of homologous type cells which agglutinated in the patient's serum at 37° C. were similarly treated, the supernatants from 37° C. aliquots being tested for warm and cold hemagglutinins (Samples D and E).

The in vitro transference of the patient's antibodies from her own cells to other normal cells was demonstrated by a method similar to one described elsewhere.<sup>10</sup> The patient's washed cells were suspended in three times their volume of normal saline and kept in a water bath at 56° C. for eight minutes with gentle agitation. The suspension was then centrifuged in cups heated to 56° C. and the supernatant was removed. Each eluate was divided into three portions. To each was added an equal portion of a washed suspension of normal group O cells. The three suspensions were kept for 12 hours at 8°, 24°, and 37° with intermittent agitation. Following this, the cells were washed with warm saline and suspended in 30 per cent bovine serum albumin. Readings were made after a two hour period of incubation.

The Ham, Donath-Landsteiner, serum bilirubin and osmotic fragility tests were performed according to standard technics.<sup>11, 12, 13, 14</sup> The effect of carbon dioxide was studied according to a previously described method.<sup>15</sup>

### CASE REPORT

L. M. was a 43 year old colored housewife admitted in a comatose state via the Johns Hopkins Hospital accident room to the gynecological service. Relatives stated that the patient's *chief complaint* had been vaginal bleeding. A more adequate history obtained later showed the *family* and *past histories* to be non-contributory. The present illness began approximately 10 days prior to admission with intermittent vaginal bleeding. The degree of bleeding could not be obtained from the history. The patient denied hemoptysis, hematemesis, epistaxis, melena, hematuria or jaundice. She had no joint or abdominal pains, or leg ulcers. An adequate dietary history was unobtainable. There had been no apparent exposure to any unusual chemicals or drugs. The patient became extremely weak several days prior to her admission and, approximately 36 hours prior to being seen at the hospital, had been lethargic and relatively unresponsive. She was brought to the hospital and admitted to the gynecological service. *Physical examination* showed a temperature of 100°, a pulse rate of 122, a respiratory rate of 16, a systolic blood pressure of 130 and diastolic pressure of 60 mm. of mercury. The skin showed evidence of recent weight loss. No edema or petechiae were present. There were three superficial excoriated ulcers approximately 1.5 cm. in diameter on the knuckle of the right first finger, one on the right buttocks, and one on the inner aspect of the right thigh. The mucous membranes showed marked pallor. There was no glandular enlargement. The pupils were dilated and the eyes fixed. The media were clear and the optic discs and vessels were normal. In both fundi were round and flame-shaped hemorrhages with occasional Roth spots. There was no sinus or mastoid tenderness. The nasal septum was intact. The patient was partially edentulous and the few remaining teeth were carious. The tongue showed normal markings. The pharynx was not injected. The neck was supple. The trachea was in the midline and there was no tracheal tug. The cervical vessels were not distended. The breasts were pendulous and atrophic. Both lungs were clear to percussion and auscultation. There was no sternal tenderness. The precordial dullness was not increased. Heart sounds were of normal quality, and the rate was rapid. There was a presystolic gallop rhythm at the mitral area and the apex. No significant murmurs were heard. There was no abdominal tenderness or palpable organs or masses. There was no costo-vertebral angle tenderness. Pelvic examination revealed no discharge or unusual bleeding. The cervix was lacerated and the uterus felt slightly enlarged. No adnexae were palpable. The mucosa of the cervix and vagina showed a few small (1 to 3 cm.) whitish patches. The rectal examination revealed nothing unusual. The appendages showed no lesions other than those already described. The neurological examination was negative. The *laboratory* data showed a negative serological test for syphilis. There was a red cell count of 550,000 per cu. mm. Hemoglobin was 1.8 grams per 100 c.c. There were 22,000 leukocytes per cu. mm. The urine showed no abnormalities. The icterus index was 10. The differential count showed 6 per cent metamyelocytes, 82 per cent polymorphonuclear neutrophils, 10 per cent lymphocytes, 2 per cent monocytes and numerous normoblasts. Vaginal cultures and blood cultures were negative.

Within the first 12 hours of the patient's stay in the hospital, 2,000 c.c. of group O blood were transfused with no apparent untoward clinical reaction. She regained consciousness and was apparently as rational as usual. Further laboratory studies performed several days after admission showed a serum non-protein nitrogen of 33 mg. per 100 c.c. Reticulocytes were 2.6 per cent. The red cell count was 2.08 million per



cu. mm. and the hemoglobin 6.2 grams per 100 c.c. The hematocrit was 20 per cent. The mean corpuscular volume was 96 cubic microns. The mean corpuscular hemoglobin concentration was 31 per cent. There were 6,350 leukocytes per cu. mm. There appeared to be slight increase in the platelets. The icterus index was 12. There was moderate anisocytosis and slight poikilocytosis. The osmotic fragility was normal. Warm auto- and isohemagglutinins were not demonstrable in the patient's serum on the second day after admission nor were there cold hemagglutinins present in



FIG. 1a. Thrombi in pulmonary vessels at various stages of formation and organization.

significant titer (table 1). The patient was thought to have marked anemia as a sequel to severe vaginal bleeding. The cause of the blood loss was not definitely ascertained. The patient was discharged on the eleventh hospital day.

She was seen in the dispensary one month after the beginning of her illness. At that time her hemoglobin was 6.2 grams per 100 c.c. The erythrocytes could not be counted because of marked autohemagglutination. The osmotic fragility was again

normal. The icterus index was 13. Four nucleated red cells were seen per 100 leukocytes. The patient was asymptomatic. However, she was admitted to the medical service one week later because of rapidly progressing weakness and "nervousness." There was no history of blood loss. Again the patient showed marked pallor. With the exception of her mental status there was only one essential change in physical examination from the time of her first admission, i.e., slight jaundice was



FIG. 1b.

noted. Laboratory data showed a high titer of autohemagglutinins at icebox temperature. The hemoglobin had fallen to 2.9 grams per 100 c.c. and the hematocrit was 9 per cent. The reticulocyte count was 21 per cent. There were 13,850 leukocytes per cu. mm. The icterus index was 23. No unusual leukocytes were noted on the blood smear. There were 6 nucleated red cells per 100 leukocytes. Sickling

preparations were negative. The urine showed a specific gravity of 1.016 and contained a trace of albumin. Urobilinogen in the urine was detectable in a dilution of 1 to 160. Otherwise the urine was normal. Prothrombin time was 23 seconds (greater than 50 per cent of normal). Serum non-protein nitrogen was 28 mg. per 100 c.c. Total serum protein was 7.69 grams per 100 c.c. Total serum bilirubin was 3.9 mg. per 100 c.c. with 0.9 mg. of the direct reacting type. Blood cholesterol was



FIG. 1c.

200 mg. per 100 c.c. Serum calcium was 9.9 mg. per 100 c.c., phosphorus 3.3 mg. per 100 c.c., and the alkaline phosphatase activity 2.5 units. The bromsulfonephthalein test showed 28 per cent retention at the end of 30 minutes (normal 0 to 5 per cent retention). Thymol turbidity was 11.4 units (normal 0 to 6 units) and the cephalin flocculation test was two plus. Roentgen-rays of the bones showed no lesions.

Sternal puncture showed only an increased percentage of normoblasts. Donath-Landsteiner and Ham tests were negative. No hemolytic activity of the serum was demonstrable with carbon dioxide by a technic described elsewhere.<sup>15</sup> A night specimen of urine was negative for hemoglobin by spectroscopic examination and negative for hemosiderin.<sup>16</sup> Cold hemagglutinins were present in a titer of 3,072 units. A bladder culture and a blood culture were both negative.

The patient responded well to numerous transfusions and experienced no apparent clinical transfusion reactions. Her cold hemagglutinin titer remained over 2,048 units. As repeated blood transfusions were necessary to maintain a satisfactory hemoglobin level, a splenectomy was considered advisable. The spleen, removed two and one half-months after the beginning of her illness, weighed 350 grams. Microscopically there were numerous large malpighian bodies. There was no dilatation of the sinuses or engorgement of the pulp. There were numerous mononuclear cells in the perilymphatic tissues. Thirty-three days following splenectomy the cold hemagglutinin titer was 96 units but for the first time a warm autohemagglutinin in a titer of 4 units was demonstrable.

In the five weeks that followed splenectomy, it was found that the patient still required transfusions and in this period she received a total of 10 liters of blood without apparent clinical reaction. The hemoglobin attained a level of 9 grams and remained there for four weeks at which time she was discharged apparently improved. At the time of discharge a moderate glandular enlargement was noted and the liver was enlarged three fingers' breadth below the costal margin. The reticulocyte count was 16 per cent. The total bilirubin was 2.3 mg. per 100 c.c. with 1.1 mg. of the direct reacting type. Thymol turbidity was 11.8 units and the cephalin flocculation test was two plus. A test for heterophile antibodies was negative.

One month following the second discharge, the patient was seen in the dispensary acutely and critically ill. She had suddenly become quite weak and prostrate 24 hours previously. This was associated with extreme dyspnea. The physical examination showed a temperature of 102.4°, pulse rate of 136, respiratory rate of 52, systolic blood pressure 150 and diastolic 70 mm. of mercury. The patient was critically ill and the degree of dyspnea was out of proportion to her other symptoms. She was perspiring freely. There were marked pallor and slight icterus. Otherwise the examination showed no essential changes. The hemoglobin was 3 grams per 100 c.c. and the hematocrit was 17.6 per cent. The reticulocyte count was 50 per cent. Icterus index was 80. Leukocytes were 35,000 per cu. mm. On differential count there were 70 per cent polymorphonuclear neutrophils, 23 per cent lymphocytes, and 7 per cent monocytes. There were 105 normoblasts per 100 leukocytes. There was marked aniso- and macrocytosis. Autohemagglutination was so great that it was grossly visible in the syringe used for venipuncture. The patient was given 1,500 c.c. of homologous type blood warmed at 37.5° C. This was done because of the high titer of cold hemagglutinin previously observed.

The tachycardia, tachypnea, and dyspnea continued. A friction rub became audible over the left posterior chest 24 hours after admission. On the second hospital day respirations suddenly ceased. Serum obtained from the patient on the last admission and before transfusions showed a cold hemagglutinin titer of 4,096 units, and a warm autohemagglutinin titer of 64 units. The clinical impression was severe hemolytic anemia associated with extensive intravascular agglutination and thromboses.

*Autopsy* (performed by Dr. Morgan Berthrong): The body at autopsy showed evidence of recent weight loss. The skin was clear. The sclerae were icteric. Moderate generalized glandular enlargement was noted. The peritoneal cavity contained 100 c.c. of cloudy yellow fluid; the peritoneal surfaces were smooth and glistening and showed no evidence of inflammation. In the thoracic cavity were fresh soft fibrous adhesions over the lower lobes of both lungs, particularly over the diaphragmatic surfaces.

The heart was not enlarged. Both epicardium and endocardium were smooth. The valves were delicate. The myocardium was homogeneous and of good color. On the pleura of the left lung were numerous lymphoid follicles and a few patches of fibrous roughening over its upper lobe. On section there was an amazing prominence of pulmonary vessels all of which contained red clots. The vessels at the periphery of the lung were dilated in the posterior and anterior portions. Posterior portions of the lower lobe contained a gelatinous edema coagulum. On the right there was a red clot in the main pulmonary artery. On section the right lung duplicated the left in appearance.

The liver was enlarged, weighing 2,100 grams, and showed distinct rusty pigmentation. The gall-bladder appeared normal but contained two pigmented stones. The pancreas on section contained prominent vessels filled with red clots. The kidneys were firm and the capsule adhered somewhat to the kidney surfaces. Kidney architecture was normal on section but definite rusty pigmentation of the renal parenchyma was seen; this was deeper in the cortex than in the pyramids. The cervix was lacerated and the vagina was roughened by hemorrhagic material. The uterus showed dilated vessels filled with clots. The uterine muscle was homogeneous. No joint or bone marrow abnormalities were noted grossly.

On microscopic section the lungs presented a striking appearance (see photographs). The vessels were extremely prominent and were plugged by numerous thrombi, both fresh and organizing. The capillaries of the alveolar walls were markedly distended by thrombi. The alveoli contained small amounts of protein precipitate. Microscopic sections of the liver showed a central necrosis of the hepatic tissue. Thrombi were also present in the smaller vessels of other organs, particularly the pancreas. Bone marrow sections showed marked hyperplasia of the erythrocytic series.

### EXPERIMENTS AND OBSERVATIONS

As shown in table 1 there was a rising titer of cold and warm autohemagglutinins during the patient's clinical course. The first three serum studies showed no warm iso- or autohemagglutinins, although the cold hemagglutinin titer became quite high. Thirty-three days after splenectomy, and after numerous transfusions of type O and A Rh positive blood, examination of a fourth serum specimen demonstrated a decrease in cold autohemagglutinin titer. However, for the first time a warm autohemagglutinin in low titer was demonstrable. Furthermore, a warm isohemagglutinin effective against one of 24 bloods (type A<sub>1</sub> Rh<sub>2</sub> MN) was demonstrable in a titer of two units. Three months after splenec-

TABLE I

Titers of Cold and Warm Hemagglutinins at Various Times during the Clinical Course

Agglutinins Active at	Titers for Cold and Warm Autohemagglutinins Patient's Serum Against a 2% Saline Suspension of Her Own Cells (Titer Readings Designate Units)				
	Dates on Which Specimens Were Collected				
	12/31/46	2/3/47	2/12/47	3/25/47*	5/19/47
8° C	16	3072	2048	96	4096
37° C	0	0	0	4	64

\* Thirty-three days postsplenectomy.

tomy, the patient's warm auto- and isohemagglutinin titer had risen to 64 units and the cold hemagglutinin titer was 4,096 units.

The separability of the cold and warm hemagglutinins (on the sample obtained at the last admission before transfusions) was demonstrated as follows: (1) When tested against a panel of bloods the cold hemagglutinin showed no specificity for red cells (it was a panhemagglutinin) but the warm hemagglutinin showed definite specificity (table 2). Table 2 illustrates that the agglutinative pattern of the atypical warm isohemagglutinin in the patient's serum, when tested against a panel of bloods, was not predictable on the basis of the A ( $A_1$  and  $A_2$ ), O, M, N, Rh, or Hr blood types. By testing her serum with various combinations of A and O red cells which had been further subtyped with M, N, Rh, Rh', and Rh'' sera, it was found that 63 per cent of 156 different bloods were agglutinated. (2) Cells not agglutinable at 37° C. were reversibly agglutinable at icebox temperature. Adsorption experiments with agglutinable and non-agglutinable (at 37° C.) homologous red blood cells were then performed, as described under "Materials and Methods."

TABLE II

Presentation of Data on Agglutinogens Studied. There was no apparent relationship between the agglutinating activity of the patient's serum and the agglutinogens recorded.

Type of Cell	Reaction of Patient's Serum (blood type $A_1$ N Rh <sub>1</sub> ) with Various Red Blood Cell Types at 37° C. (sample of 5/19/47)	
	Reaction with Serum of Patient Positive	Negative
O	42	31
$A_1$	36	7
$A_2$	8	4
M	10	2
N	7	8
Rh <sub>1</sub>	23	8
Rh <sub>2</sub>	5	1
Rh <sub>0</sub>	2	3
Rh''	1	0
Rh negative (Hr positive)	15	5
Total	149	69

Separation of the warm from the cold hemagglutinin was possible by means of adsorption technics (table 3). When cells showing no agglutination at 37° C. were incubated with the patient's serum at 37° C., titration of the supernatant (Sample A) at 8° C. demonstrated the presence of cold hemagglutinins. When adsorption was carried out at 8° C., titration of the supernatant (Sample B) at 8° C. showed no agglutination, i.e., the cold hemagglutinin had been adsorbed. However, when the supernatant (Sample C) was titered at 37° C. with cells previously known to have been agglutinated by the serum at 37° C. warm agglutinins were still demonstrable. Hence, the cold hemagglutinin was adsorbed but the warm hemagglutinin remained intact. When agglutinable (at 37° C.)  $A_1$  Rh<sub>1</sub> red cells were incubated with the patient's serum at 37° C. for two hours with intermittent agitation and the supernatant removed after centrifugation, the serum (Sample D) no longer reacted with cells previously agglutinated at 37° C., i.e., the warm hemagglutinin had been adsorbed. However, the same aliquot (Sample E) was still positive in considerable titer against both agglutinable cells

and non-agglutinable cells (at 37° C.) when the titrations were incubated at 8° C. When this adsorbed serum was set up qualitatively against a panel of 10 bloods (typed for A<sub>1</sub>, A<sub>2</sub>, O, M, N, Rh and subtypes) both at 8° and 37° C., agglutination occurred with all bloods incubated at 8° C. but with none of the bloods incubated at 37° C. Thus it was possible to adsorb the warm hemagglutinin from the patient's serum but at the same time leave the cold hemagglutinin intact.

TABLE III  
Presentation of Data Showing Separability of Cold and Warm Hemagglutinins

Summary of Adsorption Experiments Using Patient's Serum and Appropriate Cells			
Thermal Reactivity of Cells Employed for Adsorption	Patient's Adsorbed Serum		Reaction of Test Cell with Adsorbed Serum
	Temperature at Which Adsorption Was Done	Adsorbed Supernatant Titered for	
Agglutination at 8° C. No agglutination at 37° C.	A. 37° C. B. 8° C. C. 8° C.	cold hemagglutinins cold hemagglutinins warm hemagglutinins	4 plus negative 4 plus
Agglutination at 8° C. and 37° C.	D. 37° C. E. 37° C.	warm hemagglutinins cold hemagglutinins	negative 4 plus

Elution experiments (described under "Materials and Methods") demonstrated that it was possible passively to transfer the hemagglutinins to normal red blood cells. Following sensitization of normal red cells with the eluate from the patient's heated cells, the addition of 30 per cent bovine serum albumin resulted in agglutination of the cells at 8°, 24° and 37° C.

### DISCUSSION

There are two aspects of the clinico-pathological picture exhibited by this patient which are worthy of detailed consideration. The first is a consideration of the possible rôle of autohemagglutination and thrombosis in the etiology of the hemolytic anemia and the second is a consideration of the immunological aspects of the agglutinins found in this patient.

The association of agglutination of red blood cells with resulting increased fragility has been previously demonstrated.<sup>18</sup> Hemoglobinemia and hemoglobi-nuria have been produced in two patients with high titers of cold hemagglutinins by exposure of a limb to cold.<sup>19, 20</sup> Such observations as well as the hemolytic anemias of atypical pneumonia<sup>21</sup> have suggested to others<sup>22</sup> that the "cohesion of erythrocytes may lead to their prompt mechanical destruction while in motion in the circulation." Thus intravascular agglutination may conceivably have resulted in hemolysis in this case.

Ham and Castle<sup>23, 24, 25</sup> have repeatedly suggested other mechanisms associated with red blood cell agglutination that would contribute toward or acutely cause hemolysis. As has been indicated in this case and suggested by other clinical observation,<sup>26</sup> intravascular erythrosthesis occurred in small vessels. In vivo experiments by Emerson et al.<sup>27</sup> have demonstrated that intrasplenic stasis may



be associated with localized hemoconcentration and followed by increased hypotonic fragility of red blood cells. Concanavallin A, in low concentration, causes agglutination but not a significant degree of hemolysis or alteration in hypotonic fragility of red blood cells under certain specified *in vitro* conditions.<sup>23</sup> However, the injection of this material into dogs and rabbits causes agglutination of red blood cells associated with a rapid drop in hematocrit suggesting a trapping and concentration of cells in small vessels of the body. Following such injections cells appearing in the periphery show increased hypotonic fragility. The appearance of these cells is associated with hemolytic anemias of various degrees, sometimes fatal. It has been suggested that the mechanism of erythrosthesis and localized hemoconcentration are comparable in their effects to the effects of sterile *in vitro* incubation.<sup>24, 27</sup> Following the latter procedure red blood cells show spherocytic tendencies, increased hypotonic fragility and increased cell volume. These investigators have carried their reasoning one step further and suggested that increased degrees of erythrosthesis that occur in the spleen may cause increased destruction of blood in congenital hemolytic icterus, icterus neonatorum, acute hemolytic anemias associated with sulfonamides, etc.<sup>24, 27</sup> Certainly if an increased degree of erythrosthesis is of importance in blood destruction the degree of stasis occurring in this case should play a primary rôle in the hemolytic anemia observed.

The autohemagglutination observed in the present case was marked. As the patient's condition progressed, the presence of a hemagglutinin active even at 37° C. became evident in relatively high titers. That such hemagglutinins were active *in vivo* was suggested by several observations. Venipuncture of the patient was attended by gross clumping of her erythrocytes in the warm syringe. In the latter part of her illness warming the syringe to body temperature prior to venipuncture did not lessen this clumping tendency. The second observation which suggested *in vivo* agglutination and even multiple thromboses was the extreme dyspnea and tachypnea of the patient. This was strikingly out of proportion to her physical signs. Soon after admission the patient developed a pleural friction rub. This clinical picture suggested the possibility of multiple pulmonary thromboses.

This clinical impression was verified at autopsy, where the lungs presented a striking appearance. The vessels were extremely prominent and were plugged by numerous thrombi. Microscopically the degree of thrombosis was even more impressive (see photographs). The capillaries of the alveolar walls were markedly distended by thrombi and under low power resembled a heavy wire mesh. The remainder of the histological structure of the alveolar walls was obliterated by the distended capillaries. The alveoli contained a small amount of protein precipitate which suggested some pulmonary edema. It seems logical to assume that the autohemagglutination accounted for the extensive multiple thromboses. If *in vivo* autohemagglutination leads to hemolysis, then these observations would indicate adequate cause for the fatal hemolytic crisis of this patient.

The observations of Granick<sup>28</sup> on horse spleen bear on the Castle-Ham concept. By the production of a black insoluble iron sulfide Granick studied the distribution of inorganic iron. Examination of freshly teased horse spleen revealed spherocytes and large red blood cells containing diffuse inorganic iron.<sup>29</sup> This observation was interpreted as indicating intraerythrocytic disintegration of the heme molecule in the spleen. As normal horse blood may contain amounts



of ferrihemoglobin in the order of 20 per cent of the total hemoglobin present<sup>30</sup> it was suggested by Granick that the spleen of the horse may have oxidative effects on erythrocytes stagnant in its sinuses resulting in their eventual lysis.

The second aspect of this case worthy of study pertains to the immunological characteristics of the patient's serum.

"Polyagglutinability" is a term applied by some<sup>31</sup> to changes in agglutinability of erythrocytes following in vitro contamination with bacteria. Such exposure of cells may render them agglutinable to normal serum. This has been termed the "Heubner-Thomsen-Freidenreich phenomenon." Levine and Katzin<sup>32</sup> have described observations which suggest that a somewhat similar phenomenon may occur in vivo. They reported the case of a four-year-old child who had measles complicated by bronchopneumonia, and empyema due to a pneumococcus Type I. Although the patient had group O red blood cells, 15 per cent of various serums, irrespective of blood group, agglutinated them. However, no unusual agglutinin was described in the patient's serum. The effective agglutinin present in 15 per cent of the population was adsorbable by the patient's cells. Four months after the illness the cells of the patient no longer possessed this ability. Sachs and Gaffney<sup>31</sup> reported two cases in which the red cells showed polyagglutinability. The cells (group O) of one patient were agglutinated by 89 per cent of normal serums in dilutions of 1 to 16 and 1 to 32 at room temperature and refrigerator temperature respectively. The changes observed in the present patient differ from the above characteristics of polyagglutinability. In the first place, the serums of the above mentioned patients did not contain the effective agglutinin. Furthermore, the phenomenon of polyagglutinability does not occur at 37° C., but only at lower temperatures (25° C. or below).

Neter<sup>33</sup> has reported a 26 year old male patient with a *Streptococcus viridans* endocarditis who, after three whole blood transfusions, developed an irregular isohemagglutinin which was effective against 20 per cent of group O red blood cells at icebox temperature and at 37° C. The isohemagglutinin was present only in a titer of 1 to 2 and could not be demonstrated late in the disease process.

The occurrence of cold hemagglutinins in hemolytic anemias has been demonstrated by Boorman,<sup>8</sup> Finland,<sup>34</sup> McSweeney,<sup>35</sup> and Siebens.<sup>36</sup> It has been suggested by Wiener,<sup>2</sup> Baar,<sup>3</sup> Reisner and Kalkstein,<sup>1</sup> and Young<sup>37</sup> that the warm hemagglutinins developing in some cases of hemolytic anemias were cold hemagglutinins which attained a thermal amplitude of 37° C. In the present case, it appears from the available data that at least two separate atypical serological components were present: (1) a non-specific panhemagglutinin which reacted only at icebox temperature and (2) a hemagglutinin which reacted with the patient's cells and 63 per cent of red cell samples from group A and O bloods; whether the capacity to agglutinate the patient's own, in addition to other red blood cells, represents the action of more than the described components is not known. These atypical hemagglutinins occurred in addition to the naturally occurring anti-B hemagglutinin which was present in a demonstrable titer of 64 units. The separability of the two atypical hemagglutinins was suggested first by the difference in time of appearance and second by the independence in fluctuation in concentration. When the warm hemagglutinin titer was first demonstrable the cold hemagglutinin titer was much lower than it had been on previous occasions. Subsequently the warm hemagglutinin titer rose to higher

levels while the cold hemagglutinin titer did not rise much above the previous point it attained (at which time no warm hemagglutinin titer was demonstrable). The presence of qualitative differences was established by the following facts. A hemagglutinin reacting with and adsorbed by the patient's own cells at 37° C. also agglutinated 63 per cent of normal red cells from 156 group A and O blood samples at 37° C. A panhemagglutinin active only in the cold (cold hemagglutinin) was also present. Adsorption experiments proved the separability of the atypical warm cell-specific hemagglutinin from the non-specific cold hemagglutinin. Since the warm hemagglutinin was not adsorbed non-specifically by red cells that were unagglutinated (at 37° C.) by the serum, and the warm hemagglutinin was independent of known blood groups, it is possible that it was specific for an unknown agglutigen contained in certain of the normal red cells and those of the patient.

Young<sup>38</sup> has pointed out that patients of blood groups A and AB may develop increased  $\alpha_1$  or  $\alpha_2$  isohemagglutinin titers following transfusions of the heterologous type A blood and thus develop a possible hemolytic reaction on this account. That such isohemagglutinins cannot account for the observations made in this patient is apparent from study of table 2. The serum of the patient gave both positive and negative reactions with a series of A<sub>1</sub> and A<sub>2</sub> bloods in which the possible effects of other known blood group antigens were excluded with a few rare exceptions which are noted below.

Wiener<sup>39, 40</sup> observed the development of anti-P hemagglutinins in two post-transfusion serums. Anti-P serum was not available for the study of this case. However, the ratio of positive to negative reactions did not concur with the ratios obtained by Dahr<sup>41</sup> in his study of P positive and P negative individuals. Furthermore, anti-P agglutinins are usually quite weak and react most distinctly at low temperatures. That the present warm agglutinin is identical with the anti-X of Andresen<sup>42</sup> would seem highly unlikely on purely a statistical basis. As was pointed out originally, 94 per cent of human erythrocytes contain X agglutigen. Only 63 per cent of the panel of bloods reacted to the warm hemagglutinin present in this case.

Callender et al.<sup>43</sup> have observed the development of warm atypical isohemagglutinins following multiple transfusions. In an anemia patient who had received repeated transfusions, they were able to identify four isohemagglutinins. One hemagglutinin, designated after the donor's name as anti-Lutheran, agglutinated 8 to 9 per cent of several hundred bloods regardless of A, B, O, M, N, P, or Rh types. They demonstrated that the Lutheran agglutigen was inherited as a Mendelian dominant. Three other antibodies subsequently appeared in the patient's serum following further transfusions; anti-St, anti-Willis, and anti-Levay. Willis antigen was found in 7 per cent of the British population as a Mendelian dominant inherited in a manner relating to Rh but not to A, B, O, M, N, or P. The Levay antigen was found only in the blood of one of the donors and his father. Several hundred bloods examined at random did not show this hemagglutigen.

#### SUMMARY

1. The present case is that of a patient who developed during observation two atypical hemagglutinins in high titer associated with multiple transfusions.

2. A non-specific panhemagglutinin was observed (cold hemagglutinin) which reacted with, and was adsorbed by, all types of cells tested including those of the patient at low temperature.

3. A warm hemagglutinin was demonstrated which reacted at 37° C. with the patient's cells and those of 63 per cent of bloods compatible for A<sub>1</sub>, A<sub>2</sub>, O, M, N, Rr, and Hr. It could be adsorbed only by those cells agglutinated by it at 37° C. This hemagglutinin was possibly specific for an unidentified agglutinin, one apparently present in the patient's own cells.

4. The patient developed a severe hemolytic anemia, characterized by hyperbilirubinemia, reticulocytosis, nucleated red cells, and generalized intravascular thrombosis. It is suggested that the autohemagglutination contributed to the intravascular thromboses and that both factors may have produced erythrosthesis with further increase in blood destruction.

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**OBSERVATIONS ON THE FATE OF THE ACCESSORY CONDUCTOR IN WOLFF-PARKINSON-WHITE SYNDROME:  
REPORT OF A CASE DEMONSTRATING RETURN  
TO NORMAL CONDUCTION FOLLOWING  
ACUTE ILLNESS \***

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THE electrocardiographic syndrome of Wolff, Parkinson and White <sup>7</sup> is commonly believed to result from the presence in the heart of an accessory atrio-ventricular conducting structure similar to the Bundle of Kent of some animals. This serves as a short-circuiting device around the normal A-V system and delivers the impulse prematurely to one ventricle, usually the right. The resulting electrocardiographic pattern is that of bundle branch block with a short P-R interval. The mechanism was first suggested by Holzman and Scherf <sup>5</sup> and by Wolferth and Wood <sup>6</sup>; it was duplicated experimentally by Butterworth <sup>2</sup> and demonstrated histologically by Wood, Wolferth and Geckler <sup>8</sup> in a child who during life exhibited this curious syndrome.

Although it has been noted in an infant of 14 weeks <sup>1</sup> (who also had coarctation of the aorta) and occasionally in subjects of middle age, this condition is most commonly encountered in young adult males. Most cases recently have been reported from the armed forces. In spite of isolated exceptions, one gets the impression from the literature that Wolff-Parkinson-White syndrome occurs largely in young adult males as the result of an anomaly which is present at birth. Additionally, it would appear that the electrocardiographic stigmata tend to disappear with advancing years. This is apparent from the almost total absence of the syndrome among the aged and is even more striking when one recalls that, by and large, the greatest number of electrocardiograms are made on older subjects. Contrariwise, the low incidence of this anomaly in the young may be partly explained by the fact that few tracings are ordinarily made on children. However, the incidence of one in 500 <sup>3</sup> to one in 400 <sup>4</sup> seen in young adults is not even remotely approached in juveniles.

We have, therefore, the curious phenomenon of an electrocardiographic syndrome in young adults which results from a congenital vestige but which is rarely

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manifest in childhood or in old age. One may, therefore, postulate that the accessory muscle bundle which is present at birth may not become operative until early adult life and then probably as the result of altered physiology of the heart and its conducting mechanisms. Such a change could come about from increased vagus activity or as the result of illness. Recent reports have stressed the comparatively high incidence of organic disease of the heart in association with Wolff-Parkinson-White syndrome. Subclinical rheumatic fever and equally obscure toxic myocarditis doubtless make this incidence even higher. It is suggested, therefore, that increasing vagus control or organic disease cause depression of the normal A-V conducting system, thus disturbing an existing equilibrium and permitting a dormant accessory pathway to assume an abnormal conducting function. If the aberrant pathway is coincidentally suppressed by the same disease no unusual conduction is expected. When the abnormal pathway retains its comparatively greater irritability and conductivity the syndrome of premature ventricular excitation becomes lasting.

Where the accessory atrioventricular channel has been functioning for some time and the syndrome of short P-R and long QRS is well established, changes in, or injury to, the conducting system may further alter the ventricular innervation. Such damage could be gradual as with progressive vascular depletion or more rapid as from acute ischemia or toxic illness. When the aberrant conductor has become sufficiently involved it recedes in activity and the normal A-V system resumes its function.

It would appear, therefore, that altered physiology of the normal conducting system or injury to it may permit an inactive vestigial pathway to assume an abnormal function of conduction and result in an electrocardiographic syndrome. Subsequently, toxic or degenerative states act to deprive the abnormal structure of that faculty and result in disappearance of the short P-R, long QRS pattern.

A case is presented which is, apparently, an instance of complete suppression of an aberrant atrioventricular conductor occurring during the course of and resulting from an acute illness.

#### CASE REPORT

A 39 year old mail carrier was admitted to the hospital on April 5, 1946 complaining of fever, chills, weakness, substernal tightness, cough and bloody sputum. The illness began three weeks earlier with chilliness, coryza and cough. He remained at work, but after two weeks became aware of weakness, fever, chest pain and weight loss. Bloody sputum was noted three days before admission. The past history was positive for the usual childhood exanthemata, scarlet fever, and gonorrhea. There was also a history of joint pains and stiffness. The family history was non-contributory.

The positive findings on physical examination were limited to the chest. Dullness was present at the right base, and numerous rhonchi and râles were heard bilaterally. The heart was normal except for tachycardia and the blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. The initial diagnosis of primary atypical pneumonia was confirmed by roentgen-ray which showed evidence of this condition bilaterally.

The temperature on admission was 101.2° F., the pulse was 124, and the respirations were 32. The white blood cell count was 10,200, hemoglobin was 12.8 grams, and the serology was negative. Subsequently the white count varied between 10,000 and 38,000 with up to 94 per cent polymorphonuclear leukocytes. Sputum

cultures revealed the presence of *Neisseria catarrhalis* and alpha streptococcus. Other cultures were positive for Pneumococcus of the "A" group and for Staphylococcus. No tubercle bacilli were ever obtained. The urine contained albumin on several occasions; the concentration was good and the sediment showed numerous white blood cells and occasional red blood cells. Two months after the onset of the illness an antistreptolysin titer was reported as showing 1550 units.

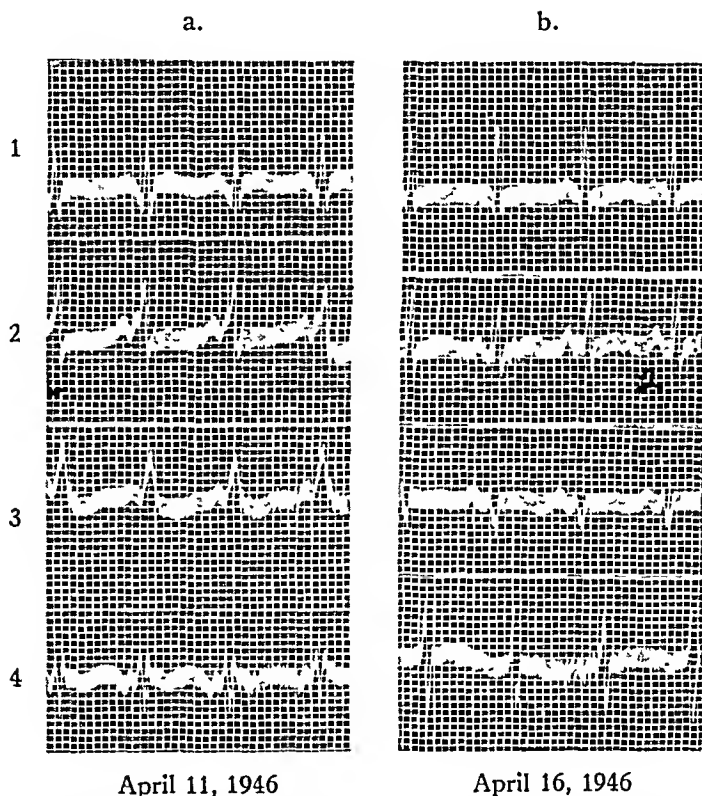


FIG. 1. *a.* Obtained on the sixth hospital day. Short P-R, long QRS pattern with rate of 136 and low-to-inverted T-waves in all leads. *b.* Made on the tenth day. Normal conduction. Rate 136, axis rotated to the left. T-waves everywhere low-to-flat.

The initial therapeutic measure consisted of the administration of 25,000 units of penicillin every three hours. On the following day the patient appeared worse and breathing was more labored. However, there were still no frank signs of consolidation. Two days later the dyspnea increased further and cyanosis was first noted. Sulfadiazine was started and the patient was put into an oxygen tent. In spite of this he suddenly went into acute vascular collapse with marked cyanosis, pulmonary edema, hyperpnea, sweating and a rapid, thready pulse. Intravenous aminophylline was given and appeared to control the seizure. On the following day the episode recurred, with respirations increasing to 60 and pulse to 160 per minute. At this time he was rapidly digitalized, kept in oxygen, and given morphine to control the tachypnea and apprehension. The cyanosis and dyspnea persisted for several days and gradually receded. During this time the patient was maintained on penicillin, cedilanid, aminophyllin, oxygen and morphine.

On the tenth day of hospitalization, although the patient felt somewhat more comfortable, roentgen-rays demonstrated extensive spread of the process bilaterally.

On the eleventh day he again went into acute collapse with evidence of gross pulmonary edema. For some time he was almost completely unresponsive but finally improved following the administration of aminophylline, coramine and oxygen by positive pressure mask.

Following the last episode of collapse, improvement was steady and no further evidence of cardiac inadequacy was ever noted. On the eighteenth day penicillin and cedilanid were discontinued and he was given bathroom privileges. There were no further setbacks and the patient proceeded to get well clinically. Subsequent roentgenographic films showed progressive clearing of the pneumonic process. No pleural or pericardial fluid was ever demonstrated and there was no enlargement, distortion or displacement of the heart. Fluoroscopy was interpreted as showing slight diminution of the cardiac excursion.

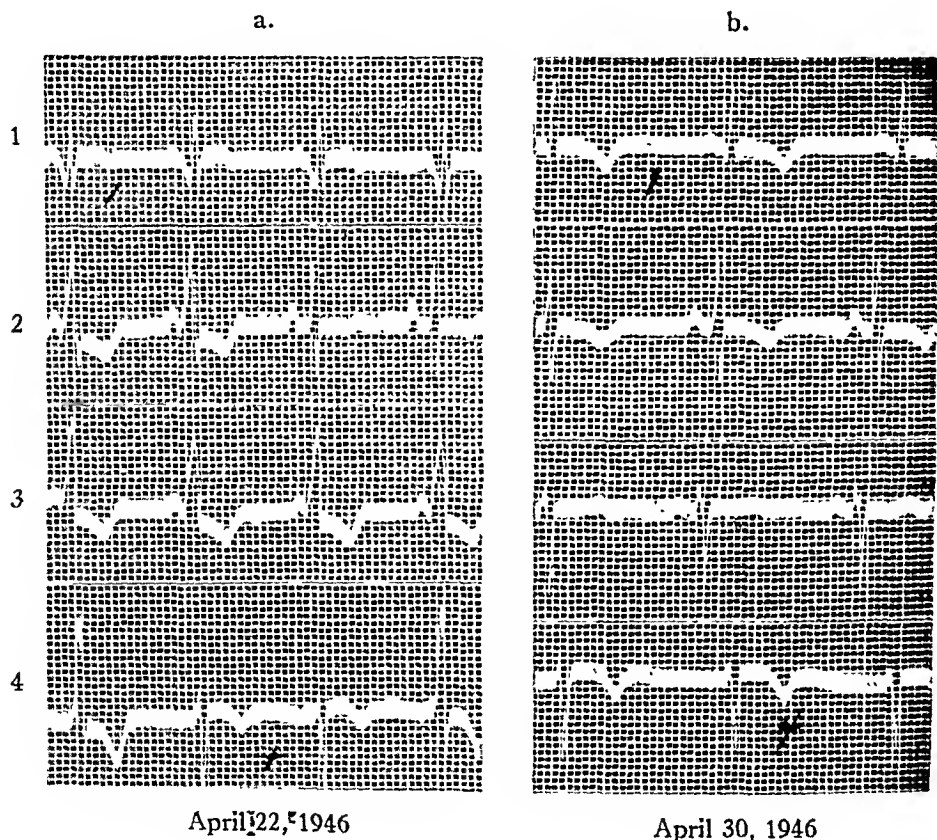


FIG. 2. *a.* Obtained on the seventeenth hospital day. Lead I: Short P-R, long QRS pattern. Lead II: The first 2 beats show abnormal conduction, the third and fourth have a normal P-R and QRS. Lead III: Abnormal throughout. Lead IVF: The first and fourth beats are abnormal; the second and third show normal conduction. However, note inverted T-waves in those beats having normal duration of QRS. *b.* Normal conduction throughout. Left axis deviation. T inverted in L1, L2 and 4F.

A long series of electrocardiograms was made beginning on the sixth day. The first of these showed marked tachycardia, low to inverted T-waves in all leads, and what appeared to be an instance of short P-R, long QRS pattern. Five days later a tracing showed normal conduction with a P-R interval of .13 second. However, the T-waves were low to flat. On the seventeenth day an electrocardiogram revealed a curious mixing of normal and abnormal impulses. Most of the ventricular com-



plexes were of the short P-R, long QRS type but a number in the second and fourth (4F) leads had a P-R interval of normal length. In those beats demonstrating a normal P-R: QRS relationship the T-waves were abnormal and were thought to represent evidence of acute myocarditis. This was the last electrocardiogram which showed any trace of abnormal impulse distribution.

On the twenty-fifth day a tracing was made which revealed a P-R interval of .12 and a QRS of .07 second. There was left axis deviation and inverted T-waves in the first, second and fourth leads. Two weeks later T<sub>1</sub> had become erect while the other leads remained unaltered. Over a period of time gradual erection of the inverted T-waves took place and the most recent graphs were entirely within normal limits. The last of these was made two years after the acute illness.

The patient subsequently returned to work and except for occasional joint pains has been entirely asymptomatic.

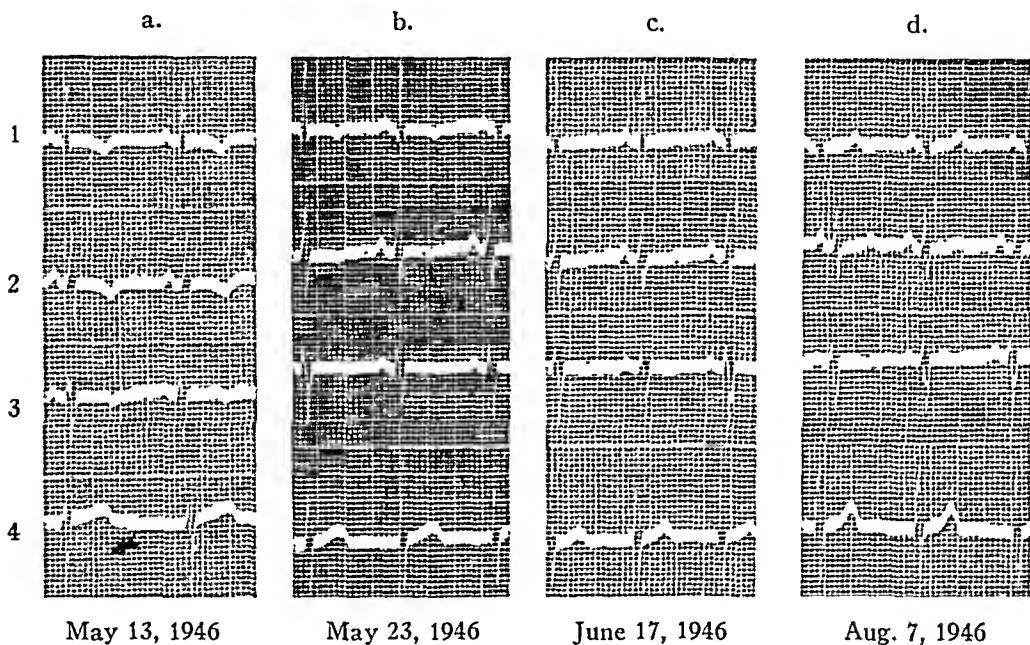


FIG. 3. Progressive recovery from myocarditis. Note gradual erection and heightening of the T-waves.

### DISCUSSION

The episodes of acute failure in this patient may have resulted from either the toxic state of the myocardium or from paroxysms of tachycardia. Unfortunately no electrocardiograms were made during the attacks so that the exact mechanism remains obscure. The high white blood count and elevated antistreptolysin titer were thought to be consistent with a streptococcus infection. However, one wonders if the illness was not actually a bizarre type of rheumatic fever with pulmonary and myocardial manifestations.

Since the first electrocardiogram in this patient showing abnormal A-V conduction was obtained when myocardial involvement was already evident, one cannot be certain that the syndrome of short P-R and long QRS was present before the illness. It is possible, therefore, that the aberrant conductor began

to function after the normal mechanism had already been suppressed. With recovery it lost its temporary advantage and normal impulse distribution recurred. In this manner it would resemble the case described by Wolferth and Wood<sup>6</sup> in which the electrocardiographic syndrome was present during active rheumatic fever but had disappeared two years later. However, it will be recalled that partial reversion to normal P-R and QRS duration occurred when the myocarditis was at its height and that electrocardiographic evidence of myocardial involvement persisted long after all vestiges of accessory conduction had disappeared. It would appear, therefore, that a functioning aberrant pathway had been completely and permanently suppressed during the course of severe, toxic myocarditis.

Although these conclusions are warranted from the evidence in this case, it is unlikely that most instances of Wolff-Parkinson-White syndrome are ended in so dramatic a manner. It is felt that more commonly progressive vascular changes lead to diminution of irritability of the vestigial pathway to the point where it ceases to be an important agent of atrioventricular conduction.

### SUMMARY

The mechanism, physiologic activity and eventual fate of the accessory atrioventricular conductor in Wolff-Parkinson-White syndrome are discussed.

A case of Wolff-Parkinson-White syndrome is presented which was first observed during the course of an acute illness with associated myocarditis. All traces of premature ventricular excitation disappeared while electrocardiographic evidence of myocarditis was still present.

It is suggested that the accessory atrioventricular conductor was completely and permanently suppressed by the toxic process.

The author expresses his gratitude to Dr. Paul D. White for his interest in and criticism of this paper.

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## VITAMIN D INTOXICATION DUE TO ERTRON: REPORT OF TWO CASES \*

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THE deleterious effects of large doses of vitamin D, although well established, have not received sufficient emphasis in the therapy of those chronic conditions, notably arthritis, for which prolonged administration of the drug has been suggested.

Danowski, Winkler, and Peters<sup>1</sup> reported two patients suffering from vitamin D intoxication, one of whom was taking vitamin D produced by the electrical activation of heat vaporized ergosterol. In both instances there was evidence of decreased renal function, and one patient exhibited soft tissue calcification. Freeman, Rhoads, and Yeager<sup>2</sup> described toxic symptoms due to hypervitaminosis D in two subjects taking Ertron. The important symptoms and signs presented were lassitude, weakness, anorexia, skin eruption, involvement of the conjunctivae, renal insufficiency, anemia, and eosinophilia.

Bauer and Freyberg<sup>3</sup> reviewed the literature and summarized the postmortem findings in five cases of hypervitaminosis D with metastatic calcification, adding one case of their own. In four instances metastatic calcification was considered to be the cause of death. These authors found the pathological changes associated with vitamin D intoxication to consist chiefly of calcification involving the arterial vascular system and the kidneys. Kaufman, Beck, and Wiseman<sup>4</sup> reported a patient developing massive metastatic tissue calcification, renal insufficiency and anemia resulting in death following Ertron therapy.

We believe that intoxication from the administration of massive doses of vitamin D is more widespread than the reports in the literature appear to indicate, for the clinical picture may masquerade as renal disease or even hyperparathyroidism. The paucity of recorded instances of injurious effects points out the need for further emphasis of this syndrome.

Two patients exhibiting hypervitaminosis D due to Ertron ingestion have been observed recently. In one renal disease was prominent, while in the other hyperparathyroidism was suggested.

### CASE REPORT

*Case 1. History:* Mrs. L. E. W., a 59-year-old housewife, was admitted to Duke Hospital on January 27, 1946, complaining of progressive weakness and lassitude of 18 months' duration and of visual disturbances for eight months. The patient was active until five years before admission at which time she developed a progressive, low-grade polyarthritis involving the hands, elbows, shoulders, back, and knees. A diagnosis of rheumatoid arthritis was made and physiotherapy was started a few months later. In January, 1941, her tonsils were removed, and this was followed by three roentgen-ray treatments to the posterior pharynx. Multiple teeth were extracted, and a submucous resection was performed in an effort to eliminate foci of infection.

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In March, 1943, vitamin D therapy in the form of Ertron capsules was begun at the suggestion of an arthritic friend. During 1943 she ingested 17,500,000 U.S.P. units (approximately 50,000 U.S.P. units daily); in 1944, 35,000,000 U.S.P. units (approximately 100,000 U.S.P. units daily); and in 1945, 60,000,000 U.S.P. units (approximately 150,000 U.S.P. units daily).<sup>\*</sup> Because of improvement in her arthritis, physiotherapy was stopped eight months before admission and Ertron was discontinued one week before admission.

Eighteen months before admission the patient noticed the onset of lassitude, weakness, anorexia, frequency with nocturia four to five times a night, and developed an anemia which failed to respond to iron, liver therapy, and two transfusions. For eight months prior to admission there had been a gradual progression of dimness and blurring of vision, photophobia, and burning of the eyes which had not responded to treatment. For four to five months prior to admission restlessness and insomnia were present. She had lost about 60 pounds in body weight during the course of her arthritis.

*Physical Examination:* The temperature was 36.4° C.; the pulse was 80 beats per minute; the respirations were 20 per minute; and the blood pressure was 150 mm. of mercury systolic and 80 mm. of mercury diastolic. The patient was a chronically ill, mentally vague, sallow complexioned, 59-year-old white female manifesting evidence of marked weight loss. The eyes showed increased pigmentation and slight puffiness of the upper lids. There was a slight bilateral ptosis which was not of the sympathetic type. Paralysis of upward gaze was present, but the extraocular muscles were otherwise normal. There was bilateral hypesthesia and associated dehydration of the cornea and conjunctiva with some areas of filamentous keratitis of the cornea. Dryness of the mouth was present which was thought to be due to recent roentgen-ray therapy. The lungs were clear. The heart was normal in size and shape. The sounds were of average intensity, and there was a soft systolic murmur at the apex. The rhythm was normal. The abdomen was not remarkable. The hands revealed fusiform swelling of all the proximal phalangeal joints and the metacarpophalangeal joints. There was slight limitation of extension of the right elbow and more marked limitation of the left. The knees were slightly enlarged without limitation of movement. Several of the finger joints exhibited firm, non-tender, freely movable, subcutaneous nodules, about 1 cm. in diameter. There was a firm, non-tender movable cystic mass in the right popliteal fossa. The reflexes and sensory system were intact.

*Laboratory Data:* The hemoglobin was 12.2 grams per cent. The red blood cell count was 4,200,000 per cu. mm. The white blood cell count was 5,100 per cu. mm. The sedimentation rate was 43 mm. in one hour corrected (Wintrobe) and the Weltmann band was 6½. The urine revealed a trace of albumin. The blood non-protein nitrogen was 55 mg. per cent. The serum calcium was 13.4 mg. per cent; the serum phosphorus was 4.4 mg. per cent; and the serum alkaline phosphatase was 3 Bodansky units. In the two-hour phenolsulfonphthalein renal excretion test 2 per cent of the dye was excreted in two hours. The maximal concentration of the urine during the Mosenthal test was 1.009. A roentgen-ray film of the chest showed the heart and lungs to be normal. A roentgenogram of the hand showed arthritic changes about the fingers of the left hand with a large amount of calcium deposited around the third and fifth fingers. There were minimal arthritic changes in the right knee. Skull films were negative. The lumbar spine, pelvis, and the left tibia showed some loss of calcium with calcification in the blood vessels of the left leg. An electrocardiogram was within normal limits.

*Course in the Hospital:* The mental cloudiness cleared somewhat during her stay in the hospital, and she was discharged on the seventeenth hospital day upon a low

<sup>\*</sup>The manufacturer has recommended as high as 300,000 U.S.P. units per day for at least one year.

calcium, low phosphorus diet, with ferrous sulfate, vitamin A ophthalmic ointment, and dark glasses.

*Follow-up:* The patient was seen during an out-patient visit in April, 1946. She reported that her nocturia had decreased to once or twice each night; there was less weakness; and her appetite and vision had improved. There had been a slight increase in the stiffness of her joints. No significant changes in the physical examination were noted.

The patient entered Duke Hospital again on the Surgical Service in May, 1946, for excision of the cystic mass in the right popliteal fossa. Microscopic examination of the cyst wall showed extensive accumulation of lymphocytes and large mononuclear cells with some fibrosis, and chemical analysis of the cyst wall was positive for cholesterol. The post-operative course was uneventful.

The patient was last seen during an out-patient visit in December, 1946. She reported general improvement with a weight gain of 15 pounds, and return of most of her former energy. There was no regression of her arthritis. Subjectively, her

TABLE I  
Laboratory Findings in Case 1

	May 1944*	January 1946	February 1946	April 1946	December 1946
Hemoglobin	12 gm. %	12.2 gm. %	10.5 gm. %	9.8 gm. %	10.9 gm. %
Red blood cell count	4.4 million	4.2 million	3.2 million	3.5 million	3.7 million
White blood cell count		5,100	6,000	5,200	3,900
Sedimentation rate (Wintrobe)		43 mm./hr.		5	47 mm./hr.
Weltmann band		6.5		5	5
Blood pressure	120/70	120/70	160/90	130/70	130/80
Basal metabolic rate	-9%	-23%			
Two-hour phenolsulfon- phthalein excretion test		2%	4.7%	12% and 13%	19% and 16%
Mosenthal urine conc. (maximum)		1.009			
Urine albumin	0	Trace	Trace	1+	1+
Urine microscopic	Neg.	Neg.	Neg.	Many fine gran. casts	Occ. hyaline and coarsely gran. cast
Blood NPN	55 mg. %	55 mg. %	60 mg. %	58 mg. %	52 mg. %
Blood urea nitrogen			36 mg. %	33 mg. %	32 mg. %
Blood urea ratio			60	57	62
Blood uric acid	4 mg. %	5.3 mg. %	3.9 mg. %	3.4 mg. %	4.2 mg. %
Serum bromides		Neg.			
Serum calcium	8.7 mg. %	13.4 mg. %	12 mg. %	8.8 mg. %	8 mg. %
Serum phosphorus	3.6 mg. %	4.4 mg. %	3.6 mg. %	3.1 mg. %	2 mg. %
Serum alkaline phosphatase (Bodansky units)	3.6	3			2
Serum cholesterol			267 mg. %		
Plasma proteins		7.6 gm. %			
Plasma albumin		4.1 gm. %			
Plasma globulin		3.5 gm. %			

\* From the University of Virginia Hospital.

eyes felt better, but no objective improvement was disclosed on examination. In addition to her previous physical findings, examinations revealed a cystic mass over the dorsum of the left hand, and the edge of the liver and the tip of the spleen were just palpable. There were no changes in the roentgen-rays of the joints.

The laboratory findings are summarized in table 1.

*Summary:* Case 1 presents the picture of a patient with rheumatoid arthritis who had been taking Ertron in large doses over a prolonged period of time with the development of weakness, lassitude, metastatic calcification, disturbance of vision, lesions of the conjunctivae, and renal insufficiency. Following the discontinuance of Ertron therapy and the institution of a low-calcium regimen, the serum calcium gradually returned to normal levels. Although some amelioration of her symptoms was noted, there was no significant improvement in renal function after 11 months of observation. This very probably indicates irreversible damage to the kidneys.

*Case 2. History:* Mrs. L. P. H., a 56-year-old white married school teacher, was first seen at Duke Hospital September 6, 1945, complaining of low-back pain of two years' duration with drowsiness, nausea, and vomiting of three weeks' duration.

The patient had complained of low-back pain since childhood, with increasing pain and stiffness in the low-back region during the past two years. A corset gave little relief. Five months before admission the patient had stopped teaching because of increasing difficulty in moving about and since then had led a sedentary life.

Five months before admission her physician prescribed three Ertron capsules (150,000 U.S.P. units) daily, and two months before admission the dosage was increased to six Ertron capsules daily (300,000 U.S.P. units). A total of 31.5 million units of Ertron was received over a period of five months without improvement.

Three weeks before admission a bromide preparation for mild hypertension was begun. During this period the patient became progressively drowsy and developed anorexia with nausea and vomiting.

*Physical Examination:* The temperature was 37° C.; the pulse was 120 beats per minute; the respirations were 18 per minute; and the blood pressure was 161 mm. of mercury systolic and 88 mm. of mercury diastolic. The patient was a well-developed, well-nourished, lethargic, white woman with thick slurred speech. The optic fundi revealed minimal tortuosity of the arterioles without exudates. A 3 by 3 by 3 cm. hard mass which displaced the trachea slightly to the right was felt at the left lower lobe of the thyroid gland. The lungs were clear. The heart was slightly enlarged to the left by percussion. The rhythm was regular. The sounds were of normal intensity without murmurs. The abdomen was not remarkable. There was diffuse tenderness over the lower thoracic and lumbar spine with moderate muscle spasm. Straight leg raising tests performed upon both sides produced low-back pain.

*Laboratory Data:* The hemoglobin was 10 gm. per cent. The red blood count was 3,200,000 cells per cu. mm. The white blood count was 5,700 cells per cu. mm. The urine was positive for albumin but negative for sugar and sediment. The serum bromides were 100 mg. per cent. The serum calcium was 13 mg. per cent; the serum phosphorus was 2.2 mg. per cent; and the serum alkaline phosphatase was 4 Bodansky units. Blood non-protein nitrogen was 56 mg. per cent with a urea nitrogen of 39.7 mg. per cent, giving a blood urea ratio of 71. The maximal concentration of the urine during the Mosenthal test was 1.009. In the two-hour phenolsulfonphthalein renal excretion test 33 per cent of the dye was excreted, and upon repetition of the test 23 per cent of the dye was excreted.

A roentgen-ray film of the chest revealed scarring in the apices and a generalized increase in pulmonary markings. The heart was slightly enlarged to the left. A

plain film of the abdomen and a gastrointestinal series were not remarkable. Films of the lumbo-sacral spine showed extreme osteoporosis and slight osteoarthritic changes.

*Course in the Hospital:* The patient remained in the hospital for 30 days. During this time Ertron and bromides were discontinued, and large amounts of sodium chloride, iron, and liver extract were given. She was placed on a fracture board with a firm mattress and given daily heat and massage, strengthening exercises, and a strong low-back corset. She improved subjectively during her hospital stay, and was instructed to continue the same regimen at home.

TABLE II  
Laboratory Findings in Case 2

	September 1945	November 1945	December 1945	March 1946
Hemoglobin	10 gm. %	13.2 gm. %	13.6 gm. %	15.4 gm. %
Red blood cell count	3.2 million	4.5 million	4.6 million	
White cell blood count	5,700	8,200	7,500	7,700
Blood pressure	160/95	180/100	155/100	170/90
Basal metabolic rate			+4%	
Two-hour phenolsulfonphthalein excretion test	33% and 23%		45%	73%
Mosenthal urine conc. (maximum)	1.009			1.019
Urine albumin	1+	Trace	Trace	Neg.
Urine microscopic	Neg.	Neg.	Neg.	Neg.
Blood NPN	56 mg. %	50 mg. %	44 mg. %	37 mg. %
Blood urea nitrogen	39.7 mg. %	25 mg. %	19 mg. %	16 mg. %
Blood urea ratio	71	50	46	44
Serum bromides	100 mg. %	Neg.		
Serum calcium	15 mg. %	12.6 mg. %	12.5 mg. %	10.1 mg. %
Serum phosphorus	2.2 mg. %	4.2 mg. %	2.2 mg. %	3.5 mg. %
Serum alkaline phosphatase (Bodansky units)	4		2.4	
Plasma proteins				6.9 gm. %
Plasma albumin				4.0 mg. %
Plasma globulin				2.9 gm. %

*Follow-up:* The patient continued this regimen at home with some improvement and returned two months later. (See table 2 for findings on this admission.) A chest film showed a slight reduction in the heart size. Roentgenograms of the spine and the right shoulder showed severe osteoporosis without cystic change. A film of the abdomen showed the kidneys to be slightly smaller than usual but no stones were visible.

It was felt that the thyroid adenoma should be removed and that the neck should be explored for the possibility of parathyroid tumor. On March 11, 1946, a subtotal thyroidectomy was performed, but no abnormal parathyroid tissue was found. Her post-operative course was uneventful.

The patient has not been available for follow-up studies since her discharge in March, 1946.

*Summary:* Case 2 presents the picture of a patient with low-back pain, who ingested large amounts of Ertron over a five-month period. On admission she exhibited no serious symptoms referable to Ertron poisoning; however, she was found to have severe renal impairment, an elevated serum calcium level, and a marked anemia. During the ensuing six months there was marked improvement of the renal function as illustrated by the increased excretion of the phenolsulfonphthalein dye in two hours, increased ability to concentrate the urine, and a return of the blood non-protein nitrogen and urea to standard levels. The blood calcium fell to a normal level, and the anemia disappeared. This case illustrates that serious kidney damage and disturbed calcium-phosphorus metabolism resulting from Ertron poisoning may be transitory if the clinical condition is recognized in time. In this respect case 1 and case 2 manifest sharp contrasts.

### DISCUSSION

Ertron is prepared by the electrical activation of heat vaporized ergosterol (Whittier process). The possible toxic effects have been minimized by its manufacturer\* who has stressed persistently a difference in toxicity between vitamin D produced by the electrical activation of heat vaporized ergosterol (Ertron) and that produced by ultra-violet irradiation. McChesney and Messer,<sup>5</sup> working with dogs, found the action of Ertron and vitamin D<sub>2</sub> to be similar in raising the serum calcium level of the blood, decreasing the fecal excretion of calcium, and increasing the urinary output of calcium. The exact mode of action of vitamin D in hypervitaminosis D has not been explained. The effect is not simply an increased absorption. Watchorn<sup>6</sup> showed that, regardless of the increased absorption, the hypercalcemia and tissue calcification are not due entirely, if at all, to increased absorption, for the amounts retained in the body are actually less than normal. Shohl,<sup>7</sup> in reviewing the physiology of hypervitaminosis D, states that when the dose is 1,000 times the therapeutic dose the deposition of minerals at the epiphysis is made at the expense of the shaft. The balances of calcium and phosphorus then become negative, and metastatic calcification takes place. In experimental animals there is weight loss, anorexia, and diarrhea; death may occur in five to 14 days. Animals which survive may show lesions for at least six months afterwards. With diets low in either calcium or phosphorus, calcification is less severe and more delayed, but the degenerative changes are as severe as those found in animals fed on normal diets.

In all cases of hypercalcemia, hypervitaminosis D should be considered in the differential diagnosis. Hyperparathyroidism, multiple myeloma, and skeletal neoplasm are three common causes of hypercalcemia. In hyperparathyroidism with definite changes in the bones the serum alkaline phosphatase is elevated. Gutman<sup>8</sup> reviewed 28 cases of hyperparathyroidism with definite changes in the bones, each of which had an elevated serum alkaline phosphatase. In 24 cases the increase was twofold or greater, and in 16 cases the increase was at least fivefold.† In the two cases of Ertron poisoning herein reported the serum alkaline phosphatase varied between two and four Bodansky units. Freeman, Rhoads, and Yeager<sup>2</sup> are the only other authors who have reported serum alkaline phos-

\* Nutrition Research Laboratories.

† The Bodansky method which Gutman utilized gives normal values of 1.5 to 4 Bodansky units.



phatase activity in Ertron poisoning. Their two patients had serum alkaline phosphatase values of 3.2 and 5.1 Bodansky units, respectively. It appears from these four cases that the absence of an elevation of serum alkaline phosphatase in Ertron poisoning to the degree that occurs commonly in hyperparathyroidism with definite bone changes may be a helpful laboratory differential diagnostic point. The history of massive vitamin D ingestion is most important in making the differential diagnosis of hypervitaminosis D in cases of hypercalcemia.

#### SUMMARY

Two cases of Ertron (activated steroids, Whittier process) poisoning are reported to emphasize that the prolonged administration of massive doses of anti-rachitic substances may produce disturbances in calcium-phosphorus metabolism with serious renal damage. Ertron therapy, therefore, is potentially dangerous.

If massive doses of such drugs are to be used in the treatment of arthritis, frequent observations must be made upon the hemoglobin, urine, renal function tests, and calcium and phosphorus blood serum levels in order to detect early intoxication and to prevent irreversible tissue changes.

In all instances of hypercalcemia, vitamin D intoxication should be considered in the differential diagnosis.

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## EDITORIAL

### ANTICOAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS

THE high and apparently increasing frequency of coronary thrombosis and myocardial infarction in our aging population as well as the dramatically abrupt onset and high mortality has emphasized the need for more effective measures of treatment. The conventional measures now in use, which are largely only supportive and symptomatic, doubtless facilitate survival in many cases, but the average mortality of about 20 per cent during the first attack manifestly leaves much to be desired.

For the underlying pathological changes in the coronary arteries little or nothing has been accomplished, and at present not much of a curative nature can be expected. Effective prophylactic measures are also in a very nebulous state. The myocardium, however, has a remarkable capacity for recuperating and adjusting itself to such an injury if the initial insult has not been too devastating. If the infarcted area is so extensive that it quickly results in severe decompensation and congestive failure, profound shock or grave arrhythmias, death will often be inevitable. A substantial number of patients, however, survive the immediate effects of the attack to succumb later as a result of extension of the original thrombus and increase in the size of the infarcted area or of thrombosis elsewhere in the coronary arteries or other vessels or of emboli in the pulmonary or systemic arteries. Many recent studies, both clinical and pathological, have emphasized the frequency and prognostic importance of such thrombo-embolic complications. These observations naturally suggested that such complications might be averted by measures which would reduce the coagulability of the blood. Although thrombosis at the site of a vascular injury must be regarded in general as a protective mechanism which serves to avert hemorrhage, in the coronary arteries the resulting occlusion constitutes a far graver risk.

The rationale of such treatment seems to be sound. It has been shown in animal experiments, e.g. by Solandt and Best,<sup>1</sup> that heparin exerts such a protective action. By injecting sodium ricinoleate into an isolated section of a dog's coronary artery which was clamped off for 10 minutes following the injection, they produced a slowly progressive thrombosis and myocardial infarction in 12 of 13 animals. In a similar series of 12 animals given sufficient heparin markedly to prolong coagulation time, infarction occurred in only one. They suggested that heparin might be useful therapeutically.

There is some direct evidence in man that the coagulability of the blood is increased after myocardial infarction. It is not possible as a rule to demonstrate this convincingly by the usual methods of determining prothrombin time, using undiluted plasma. Peters et al.,<sup>2</sup> however, utilizing diluted (12.5 per cent) plasma, found that the prothrombin time was reduced

<sup>1</sup> SOLANDT, D. Y., and BEST, C. H.: Heparin and coronary thrombosis in experimental animals, *Lancet*, 1938, ii, 130-132.

<sup>2</sup> PETERS, H. R., GUYTHER, J. R., and BRAMBEL, C. E.: Dicumarol in acute coronary thrombosis, *Jr. Am. Med. Assoc.*, 1946, cxxx, 398-402.

in 67 of 110 cases from the normal range of 85 to 100 seconds to 47 to 75 seconds. This was not always demonstrable until two to three days after the onset and was regarded as a result rather than a cause of the initial attack. It might well, however, increase the tendency to secondary thrombosis and embolism.

In some of the earlier studies on the effect of anticoagulants on thrombophlebitis in general, occasional cases of coronary thrombosis were included, but not in significant numbers. During 1946, studies were reported of three series of cases large enough to warrant some tentative conclusions.

Wright<sup>3</sup> reported a series of 76 cases of acute or recurrent coronary thrombosis with myocardial infarction treated with dicumarol. Of these, 43 (with 11 deaths) were complicated by multiple thromboses, multiple emboli or both, whereas 33 cases (with four deaths), seen during the first or second attack, were not so complicated. There was no control series, but he believed that the anticipated mortality in these groups, if they had not received dicumarol, would have been double that observed. In 38 of the 43 "complicated cases," no further manifestations of thrombosis or embolism were observed after treatment with dicumarol was instituted.

Nichol and Page<sup>4</sup> reported similar experiences in the treatment with dicumarol of 50 consecutive attacks in 44 private patients, also without controls. Although the mortality (16 per cent) was not notably reduced, all 26 cases treated during their first attack survived. In six cases that came to autopsy, no evidence of recent thrombosis or embolism was found.

The series of Peters et al.<sup>2</sup> included 60 controls with 13 deaths, six from embolism which was evident clinically; and 50 cases treated with dicumarol with two deaths, one from complicating renal disease. They also reported observations (utilizing diluted plasma) which confirm those of previous workers that digitalis increases the coagulability of the blood. They cite evidence such as the report of Askey and Neurath<sup>5</sup> that the deleterious effects of digitalis reported in cases of myocardial infarction are due to an increase in the thrombo-embolic complications rather than in ventricular fibrillation or cardiac rupture. Of 17 untreated patients (of Peters et al.) who were given digitalis because of congestive failure, nine died, chiefly from embolism. Of eight patients treated with dicumarol who were given digitalis for the same reason, one died, from associated renal disease. They believe that dicumarol not only reduced the incidence of thrombosis and embolism and lowered the mortality rate but largely eliminated the untoward effects attributed to digitalis in such patients.

In none of these series were any toxic effects noted, nor was there any significant tendency to bleed, without doubt largely because of the care with which the prothrombin time was followed.

<sup>3</sup> WRIGHT, I. S.: Experiences with dicumarol (3,3'-methylene-bis-(4 hydroxycoumarin)) in the treatment of coronary thrombosis with myocardial infarction, *Am. Heart Jr.*, 1946, xxxii, 20-31.

<sup>4</sup> NICHOL, E. S., and PAGE, S. W., JR.: Dicumarol therapy in acute coronary thrombosis; results in fifty attacks, *Jr. Florida Med. Assoc.*, 1946, xxxii, 365-370.

<sup>5</sup> ASKEY, J. M., and NEURATH, O.: Is digitalis indicated in myocardial infarction? *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1016.

Although these series were neither large enough nor sufficiently well controlled to warrant any definite conclusions, the results were so promising that the Board of Directors of the American Heart Association appointed a committee to sponsor an investigation of the subject on a large scale. This was carried out coöperatively in 16 major hospitals. One thousand cases were studied, and a preliminary report covering the first 800 cases has recently been published.<sup>6</sup>

Patients admitted on even numbered days (368) were treated in the usual way and served as controls. Those admitted on odd numbered days (432) received dicumarol in addition. The prothrombin time was determined daily by a standard method (Link-Schapiro, with undiluted plasma) before further dicumarol was administered. In general the dose was adjusted so as to prolong the prothrombin time from the normal 15 to 17 seconds to 35 seconds or a little more (by the method used), but to avoid such excessive prolongation as would cause bleeding. This corresponds to a reduction of the prothrombin activity to from 10 per cent to 20 per cent of normal. A lesser depression of activity is believed to be therapeutically ineffective. Dicumarol was continued for 30 days and when possible for 30 days after the last episode of thrombosis or embolism. It was withheld from patients with a history of a tendency to hemorrhage or with hepatic or renal disease.

The results have been subjected to statistical analysis, and they show conclusively that dicumarol significantly lowered the mortality rate and markedly reduced the frequency of thrombotic and embolic complications.

Thus the mortality of the treated group as a whole was 15 per cent, as compared with 24 per cent in the controls. The mortality in patients who did not show thrombotic or embolic complications was not notably reduced in the treated group (12 per cent, as compared with 14 per cent in the controls), but deaths preceded by such complications occurred in 10 per cent of the controls and in only 3 per cent of the treated cases.

When analyzed by week of illness, the mortality was highest during the first two weeks, but it was substantial during the third and fourth weeks. In all four weeks the mortality rate in the treated cases was significantly lower than in the control groups. When studied with reference to age, it was found that the reduction in mortality was limited largely to patients 60 years of age or older. The incidence of thrombotic complications was reduced in treated patients under 60, but a larger number of the untreated younger patients were able to survive them.

The incidence of thrombo-embolic complications was more strikingly affected than the mortality rate. In the control group they were recognized clinically in 25 per cent of the cases, as compared with 11 per cent in the "treated" group. Of the latter, in 5 per cent the complication occurred before any anticoagulant had been given or during the first three days of treatment before an adequate effect had been secured. In only 6 per cent did such complications appear after treatment had been well established.

<sup>6</sup> WRIGHT, I. S., MARPLE, C. D., and BECK, D. F.: Anticoagulant therapy of coronary thrombosis, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 1074-1079.

A critical study of these failures showed that in many instances the dose of dicumarol had not been adequate to produce the requisite prolongation of the prothrombin time. Of 38 complications occurring in treated patients for whom pertinent data were available, in only four had the prothrombin time been maintained at 30 seconds or more for three days prior to the episode.

The incidence of hemorrhage was also studied. Bleeding occurred in 6 per cent of the controls and in 12 per cent of the treated group. In 5 per cent of the latter, bleeding occurred when the patient was not receiving dicumarol or was due to other causes. Of the 30 cases of bleeding attributable to dicumarol, 15 were mild and only one was severe. This relative freedom from bleeding, however, was obtained only at the cost of systematic accurate observations of the prothrombin time. Bleeding was controlled without difficulty either by injections of a vitamin K preparation or by transfusions of fresh blood.

In 14 per cent of the treated cases, heparin was given at the start to secure an immediate effect. It was not used routinely because of the technical difficulties of administration to such patients and because the incidence of thrombotic complications is relatively low before the fourth day when dicumarol should be effective.

These observations indicate that, if facilities for determining the prothrombin time are available and are utilized, dicumarol (with or without heparin at the onset) should be administered to every patient with coronary thrombosis and myocardial infarction if no specific contraindication exists. This should be done even as late as the third week or still later if thromboembolic complications occur. To be effective, however, enough dicumarol must be given substantially to prolong the prothrombin time. Half way measures are probably quite useless. These anticoagulants will not "dissolve" a thrombus which has already formed, nor do they exert any demonstrable effect on the damaged myocardium. Their only known activity, although a potent one, is to restrict extension of the original thrombus and to prevent the formation of thrombi elsewhere, particularly of mural thrombi in the ventricles, which are such a prolific source of pulmonary and systemic emboli. If determinations of the prothrombin time can not be carried out, the risk of bleeding, if effective treatment is given, must at present be regarded as prohibitive.

There are no data to suggest that this treatment reduces the incidence of subsequent attacks of coronary thrombosis after treatment is stopped.

The possibility of averting or modifying the initial attack of coronary thrombosis by means of dicumarol has not been demonstrated. Aside from bleeding, no significant toxic effects have been reported in limited numbers of patients who have received dicumarol for long periods, even from one to three years. The impossibility in most cases of predicting an attack, however, and the cost and effort involved in following the prothrombin time in large groups for protracted periods make this impracticable at present except perhaps as a major therapeutic experiment.

## REVIEWS

*An Introduction to Gastro-Enterology.* Fourth Edition, Revised and Enlarged. By WALTER C. ALVAREZ, Professor of Medicine, University of Minnesota, The Mayo Foundation, and a Senior Consultant in the Division of Medicine, the Mayo Clinic. 903 pages; 18.5 × 26 cm. 269 illustrations. Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers, New York. 1948. Price, \$12.50.

Whether or not one fully agrees with Alvarez' viewpoint about every gastro-intestinal problem, his lucid presentations are always intriguing. His style is conversational and, unlike most medical writers, he frequently makes use of the first personal pronoun. Although this leads to some verbosity, one never has to hesitate to understand what he means, and the informality of his discussions is refreshing.

Alvarez' *Gastro-Enterology* has become a classic and this fourth edition brings up to date a comprehensive review of the literature on the physiologic background of this subspecialty of internal medicine. It makes extensive reference to work on the lower animals and at the same time correlates the results with clinical observations. Very properly the author emphasizes the maximal importance of the functions, especially the motor functions, of the small intestine. Almost the first half of the book is devoted to the normal and pathological physiology of that part of the digestive tract. "The gradient theory of the polarization of the bowel," developed and popularized by the author, receives special attention, and the experimental results and arguments that are presented are most convincing. On the other hand, many problems are left unsolved, only the established facts and theories being presented, and this is done in such a way as to be highly stimulating to the clinical investigator.

An exhaustive bibliography is appended and the 186 illustrations include photographs of the important contributors to our knowledge of the subject. The book is highly recommended and should be in the hands of every student, teacher, investigator and practitioner of internal medicine, whether or not his interests are primarily in gastrointestinal disease. It will be found particularly helpful as a background for the researches of the younger gastroenterologist.

T. GRIER MILLER, M.D.

*Cornell Conferences on Therapy.* Volume III. Edited by HARRY GOLD, M.D., Managing Editor, DAVID P. BARR, M.D., McKEEN CATTELL, M.D., EUGENE F. DuBOIS, M.D., WALTER MODELL, M.D., and RALPH R. TOMPSETT, M.D. 337 pages; 14 × 21 cm. The Macmillan Company, New York. 1948. Price, \$3.50.

If the analogy is not scrutinized too closely, this book bears the same relation to a textbook of medicine as an historical novel to a textbook of history. It is not a reference book, and it gives pleasure as well as information. It is the third of a series of Medical Annuals of great value and popularity.

Like its two prototypes, this volume contains verbatim reports of a number of conferences held in recent years at the Cornell University Medical Center. All those incorporated in this volume have appeared either in the *American Journal of Medicine* or in the *New York State Medical Journal* between May 1944 and March 1948.

The stated purpose of the Cornell conferences has been "to stimulate interest in rational therapy," and to bridge the artificial gap between Pharmacology and Therapeutics by bringing clinicians and pharmacologists together in active debate. Each conference follows a pattern: an expert in the field introduces the subject of the day, and this is followed by free and informal discussion by the multivalent assembly. With this form of presentation, no matter how carefully the material is selected, there is bound to be included a certain amount of useless and uninformative matter. Some

may wonder if it is justifiable to make such inclusive material into a book; in the same number of pages half as much information again could be compressed. But this apparent waste of space is more than made up for by the ease and pleasure with which the whole book is read. Its form endows it with a natural, informal and varying style. Many gems of practical wisdom fall from the lips of the expert engaged in impromptu discussion, which never seem to find their way into the pages of a formal text. Only in a book of this kind is the experience of specialists pooled and compared, and it is not only helpful to observe where they agree but also where they disagree; for where experts differ there is comfort in our own bewilderment.

The conferences in this volume deal with such therapeutic agents as streptomycin, protein hydrolysates, BAL and the cathartics; and with such therapeutic problems as congestive heart failure, pneumonia, barbiturate poisoning, thrombophlebitis, alcoholism, and infections of the urinary tract. More general subjects such as the dose of a drug and the management of pain due to muscle spasm are also each accorded a session. Such a book will inevitably cater to a wide range of satisfied readers.

H. J. L. M.

*The Treatment of Malignant Disease by Radium and X-Rays.* By RALSTON PATERSON. 622 pages; 17 × 25 cm. The Williams and Wilkins Co., Baltimore. 1948. Price, \$11.00.

This book is primarily for radio-therapists. The author confines his work to the treatment of malignant disease as carried out at Christie Cancer Hospital and Holt Radium Institute. There is a fine description of the principles of radiation therapy, together with the necessary technical factors, for the intelligent use of radiation. Dr. Paterson gives us the benefit of his great experience with radium. Not only does he describe the use of radium, but also gives minute details for the construction of radium applicators and radium molds. In the experience of the Institute only four types of cancer are considered curable, i.e., having an appreciable five year survival rate: cancer of the skin, the lip, uterus (both body and cervix), and breast.

Every case presented for treatment is put into one of four classes: curable, treatable, palliative, and those in which treatment is contraindicated. Dr. Paterson feels that most physicians understand the application of the last three methods, but that in the curable class physicians must be made to realize that radical radiation methods should be used. When surgery is used in malignancy, nothing short of radical surgery is now accepted even though it entails many risks—for this reason the cure rate after radical surgery is now better than that in the days before this radical principle was accepted. If the same risks be accepted for radical radiation therapy our "cure rates" will improve.

Included is a plan of organization for a radiation institute equipped to handle 1500 new cases a year, plus follow-up of all old cases.

The book ends with an outline of the present status of research into the manner by which radiations produce their biological effect.

A. G. S.

*Crystalline Enzymes.* 2nd Ed. By JOHN H. NORTHROP, MOSES KUNITZ, and ROGER M. HERRIOTT. 352 pages; 16 × 24 cm. Columbia University Press, New York. 1948. Price, \$7.50.

The material in this volume, as in the first edition, has been limited to studies made in the Laboratory of General Physiology at the Rockefeller Institute for Medical Research and to closely related work. In the ten years since the earlier edition, the number of enzymes which have been isolated and crystallized has reached 35 and the controversy over the protein nature of enzymes has been largely settled. The chemi-

cal structure responsible for activity and the question as to whether or not prosthetic groups are necessary is, however, still under discussion.

Much new material has been included in this edition. The preparation and properties of two enzymes, ribonuclease and hexokinase, and of crystalline diphtheria antitoxin have been discussed in detail. The solubility method for the determination of the purity of proteins and its superiority over electrophoresis and ultracentrifugation for the detection of more than one protein component is discussed. The formation of proteins, of enzymes, and of virus is considered as one general problem—the synthesis of proteins. The authors have presented a critical analysis of the various possible synthetic reactions for proteins and have suggested a working hypothesis for their synthesis.

This highly specialized volume is extremely valuable as a reference for those interested in this field.

M. A. A.

*Investigations on Agonal Acidosis.* By IB FABRICIUS HANSEN. 135 pages; 18.5 × 26.5 cm. Povel Branner, Copenhagen, Denmark. 1948. Price, \$3.00.

"Investigations on Agonal Acidosis" is the report of studies on the biochemical changes in the blood during the agonal state. Blood was obtained from 38 adult patients either premortally or by heart puncture immediately after death. Patients with diabetes or in uremic coma were excluded as the author was interested in the frequency of agonal acidosis in conditions other than those usually associated with acidosis. The following determinations were done: pH, CO<sub>2</sub> content, chloride, sulfate, phosphate, protein, lactic acid, acetone, pyruvic acid, total base, non-protein nitrogen, urea nitrogen, amino acids, creatinine, guanidine, oxygen capacity, oxygen content.

A fall in the pH of the blood to below pH 7 was not uncommon and occasionally this may have been the direct cause of death. The plasma bicarbonate was reduced in only about a third of the cases. An increase in lactic acid appeared as a constant agonal phenomenon while increases in sulfate, phosphate and "undetermined acids" occurred frequently. There was no definite trend in plasma chloride. Most cases showed an agonal azotemia with non-protein nitrogens ranging from 26 to 216 mg. per cent, and an increase in both amino acid nitrogen and creatinine.

This series of results constitutes the first comprehensive series of determinations of blood constituents during the agonal state and should serve as a foundation for further studies along these lines.

M. A. A.

### BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Atlas of Human Anatomy, Descriptive and Regional. Volume I: Osteology, Arthrology, Myology.* By M. W. WOERDEMAN, M.D., F.R.N.A.Sc., Professor of Anatomy and Embryology and Director of the Department of Anatomy in the University of Amsterdam. 512 pages, plus 18 pages index; 26 × 18 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$12.50.

*Blood Clotting and Allied Problems: Transactions of The First Conference, February 16-17, 1948, New York, New York.* 179 pages; 23 × 15.5 cm. (loose-leaf, paper-bound). 1948. Josiah Macy, Jr., Foundation, New York. Price, \$3.25.



*The Child in Health and Disease: A Textbook for Students and Practitioners of Medicine.* By CLIFFORD G. GRULEE, M.D., Rush Professor of Pediatrics, University of Illinois, etc., and R. CANNON ELEY, M.D., Associate in Pediatrics and Communicable Diseases, Howard University Medical School, etc. 1066 pages; 26 × 18 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$12.00.

*Cornell Conferences on Therapy—Volume III.* Edited by HARRY GOLD, Managing Editor, DAVID P. BARR, M.D., McKEEN CATTELL, M.D., EUGENE F. DUBOIS, M.D., WALTER MODELL, M.D., and RALPH R. TOMPSETT, M.D. 337 pages; 21 × 14 cm. 1948. The Macmillan Company, New York. Price, \$3.50.

*Experimental Immunochemistry.* By ELVIN A. KABAT, Ph.D., Associate Professor of Bacteriology, College of Physicians and Surgeons, Columbia University and the Neurological Institute, New York; and MANFRED M. MAYER, Ph.D., Associate Professor of Bacteriology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. With a Foreword by MICHAEL HEIDELBERGER, Ph.D., Professor of Biochemistry, College of Physicians and Surgeons, Columbia University, New York. 575 pages; 24 × 15.5 cm. 1948. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$8.75.

*Factors Regulating Blood Pressure: Transactions of the Second Conference, January 8-9, 1948, New York, New York.* Edited by B. W. ZWEIFACH and EPHRAIM SHORR, Department of Medicine, Cornell University Medical College, New York. 170 pages; 23 × 16.5 cm. (loose-leaf, paper-bound). 1948. Josiah Macy, Jr. Foundation, New York. Price, \$2.75.

*The Hormones: Physiology, Chemistry and Applications. Volume I.* Edited by GREGORY PINCUS, Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, and KENNETH V. THIMANN, Harvard University, Cambridge. 886 pages; 23.5 × 15.5 cm. 1948. Academic Press, Inc., New York. Price, \$13.50.

*The Modern Management of Gastric and Duodenal Ulcer.* Edited by F. CROXON DELLER, M.D., M.R.C.P. 227 pages; 23 × 16.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$5.50.

*The Parathyroid Glands and Metabolic Bone Disease: Selected Studies.* By FULLER ALBRIGHT, A.B., M.D., Associate Professor of Medicine, Harvard Medical School, etc., and EDWARD C. REIFENSTEIN, JR., A.B., M.D., F.A.C.P., Consultant-in-Charge, Department of Clinical Investigation, Sloan-Kettering Institute of Cancer Research, Memorial Hospital Cancer Center, New York, etc. 393 pages; 23.5 × 15.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$8.00.

*The Renal Origin of Hypertension.* By HARRY GOLDBLATT, M.D., C.M., Director, Institute for Medical Research, Cedars of Lebanon Hospital, etc. 126 pages; 23.5 × 15.5 cm. 1948. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$2.75.

*Textbook of the Rheumatic Diseases.* Edited by W. S. C. COPEMAN, O.B.E., M.D., F.R.C.P., Physician to the Rheumatism Department and Lecturer in the Medical School, West London Hospital, etc. 612 pages; 24.5 × 17 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$12.50.

# COLLEGE NEWS NOTES

## 30TH ANNUAL SESSION HOTEL ACCOMMODATIONS

Officers, Regents, Governors and Committeemen of the College, and Speakers on the Program of the 1949 Annual Session should apply for their hotel accommodations at once, if they have not already done so, to Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Instructions and application forms for reserving hotel rooms have been mailed to all members of the College. All who plan to visit New York City for the Annual Session and who have not yet reserved their rooms are urged to send their applications without delay to the Housing Bureau, The American College of Physicians, care of New York Convention Bureau, 500 Park Ave., New York 22, N. Y.

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### ATTENDANCE BY ASSOCIATES AT ANNUAL SESSION

Attendance at one or more Annual Sessions by Associates before their proposal for advancement to Fellowship is prescribed by regulations of the Board of Regents of the American College of Physicians. This regulation was temporarily discontinued during World War II from 1942 to 1946, because it became obviously impossible for Associates in the armed services to attend and because the Annual Sessions were not held during part of that time. The regulation is again in full effect. It is maintained that an Associate must display an abiding interest in the College and in internal medicine or its allied branches. There is no better way in which such an interest can be displayed than by attendance at the College's Annual Sessions, accepted as the most important postgraduate week in the field in North America.

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### 1949 A. C. P. DIRECTORY

It is important that members send promptly to the College Headquarters their pre-publication orders for the 1949 Directory of the American College of Physicians, if they have not already done so and wish to reserve copies. The Board of Regents' authorization to prepare and print the Directory for distribution next autumn is contingent upon the receipt of at least 2,000 pre-publication orders. A printed order form was mailed to all members of the College early in January. The early return of these order forms will enable the Headquarters staff to begin preparations for compiling the Directory without delay.

No Directory has been published by the College since 1941. Membership Rosters, and Supplements thereto have been distributed but these lack the biographical data which make the Directory of great usefulness to the members as well as institutions and medical organizations. The pre-publication price to members of the College will be \$4.00; to non-members, institutions and others, \$5.00.

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### REGIONAL MEETINGS OF THE AMERICAN COLLEGE OF PHYSICIANS

The *North Carolina* Regional Meeting of the College was held at the Duke University Hospital, Durham, on December 3, 1948, with a dinner at the Washington Duke Hotel. A fine attendance was experienced at this meeting which was held under the Governorship of Paul F. Whitaker, M.D., F.A.C.P., Kinston, and planned by Edward McG. Hedgpeth, M.D., F.A.C.P., chairman of the program committee, Chapel Hill, and J. Lamar Callaway, M.D., Associate, chairman of local arrangements, Durham.

The guest speakers in the evening were President Walter W. Palmer, New York City, and Mr. E. R. Loveland, Executive Secretary, Philadelphia. The following papers were presented at the Afternoon Session:

Myocardial Contusion: Report of a Case with Autopsy.

MONROE T. GILMOUR, M.D., F.A.C.P., and HORACE H. HODGES, M.D. (Associate), Charlotte.

Clinicopathologic Conference.

DAVID T. SMITH, M.D., F.A.C.P., WILEY D. FORBUS, M.D. (by invitation) and H. LEE HOWARD, M.D. (by invitation), Durham.

Panel Discussion: Jaundice.

Physiology: A. T. MILLER, JR., M.D. (by invitation).

Pathology: R. WAYNE RUNDLES, M.D. (by invitation) and LELAND D. STODDARD, M.D. (by invitation).

Differential Diagnosis: ARTHUR J. FREEDMAN, M.D. (Associate), Greensboro.

Therapy: KENNETH D. WEEKS, M.D. (Associate), Rocky Mount.

Prolapse of the Gastric Mucosa Through the Pyloric Canal into the Duodenum.

I. H. MANNING, JR., M.D., F.A.C.P., Durham.

A meeting for the *District of Columbia and Maryland* was held on February 19, 1949, at the Medical Society of the District of Columbia, Washington, D. C., under the chairmanship of Wallace M. Yater, M. D., F.A.C.P., Governor for the District. Drs. Walter W. Palmer, New York City, and George Morris Piersol, Philadelphia, President and Secretary-General of the College, respectively, and Mr. E. R. Loveland, Executive Secretary, Philadelphia, were scheduled to be guest speakers. The detailed program of the meeting had not been received at the time this notice was written.

*Nebraska* members of the College held their Regional Meeting at the Paxton Hotel, Omaha, on February 19, 1949, under the Governorship of Joseph D. McCarthy, M.D., F.A.C.P., of that city. While copy of the program of this meeting had not been received when this notice went to press, Walter L. Palmer, M.D., F.A.C.P., Chicago, Chairman of the Board of Governors, had agreed to be the dinner speaker.

Announcement of the meeting of the *Virginia* Section of the College called the members to assemble at Norfolk, Va., on February 23, 1949. The Treasurer of the College, William D. Stroud, M.D., F.A.C.P., Philadelphia, was to be the guest speaker; the scientific program was not known at the time of writing. A. Brownley Hodges, M.D., F.A.C.P., Norfolk, is currently serving as chairman of the Section, and James F. Waddill, M.D., F.A.C.P., Norfolk, as secretary. W. P. Adams, M.D., F.A.C.P., Norfolk, was chairman of the Program Committee for the meeting.

#### NEW LIFE MEMBERS

The following Fellows of the College have become Life Members. (Listed in the order of subscription. Subscriptions received up to and including January 14, 1949.)

Dr. Aaron Arkin, Chicago, Ill.

Dr. Arden Freer, Washington, D. C.

Dr. Estelle E. Kleiber, New Brunswick, N. J.

Dr. John A. Kolmer, Bala-Cynwyd, Pa.

Dr. Francis G. Blake, New Haven, Conn.

Dr. Eliot E. Foltz, Evanston, Ill.

Dr. Robert E. Driscoll, Chicago, Ill.

Dr. Lyman H. Hoyt, Boston, Mass.

Dr. Charles H. Drenckhahn, Urbana, Ill.  
 Dr. Raymond Hussey, Detroit, Mich.  
 Dr. Samuel Waldman, Brooklyn, N. Y.  
 Dr. Milton D. Bosse, Pitcairn, Pa.  
 Dr. Donald S. Smith, Pontiac, Mich.

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#### CORRECTION TO DECEMBER, 1948, NEWS NOTES

In the list of new elections to Associateship and Fellowship in the American College of Physicians, published in the December News Notes Section, the name of Dr. Joseph Post, New York, N. Y., a newly elected Fellow, was inadvertently omitted.

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#### LIBRARY CONTRIBUTION

Grateful acknowledgment is made of the kindness of Louis F. Bishop, Jr., M.D., F.A.C.P., New York, N. Y., in contributing to the College Library a copy of the biography of his father, a late Fellow of the College, entitled "Hope in Heart Disease, The Story of Louis Faugeres Bishop, M.D.," by Ruth V. Bennett, published by Dorrance & Company, Philadelphia, 1948.

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The 1949 meeting of the Southern Medical Association will be held next autumn at Cincinnati, Ohio, under the presidency of Oscar B. Hunter, M.D., F.A.C.P., Washington, D. C.

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#### POSTGRADUATE COURSE ON DIABETES

The Frank E. Bunts Educational Institute and Cleveland Clinic will present a continuation course for physicians entirely devoted to the diagnosis and management of diabetes and its complications. The course will be held on March 17, 18, and 19. Drs. Henry T. Ricketts of Chicago, John S. L. Browne of Montreal, and H. L. C. Wilkerson of the United States Public Health Service will be the out-of town guest speakers. Dr. E. Perry McCullagh is director of the course. In addition to the regular faculty of the Institute several prominent Cleveland physicians will give lectures.

Inquiries regarding the complete program and registration can be addressed to the Director of Education, Frank E. Bunts Educational Institute, 2020 East Ninety-third Street, Cleveland 6, Ohio.

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#### SPECIALTY BOARD NOTICES

AMERICAN BOARD OF INTERNAL MEDICINE, William A. Werrell, M.D., Asst. Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. Oral examinations, for which the closing date for receipt of applications was January 2, 1949, will be held in New York City, March 23, 24, and 25, before the 1949 Annual Session of the American College of Physicians, and in Philadelphia on June 1, 2, and 3, before the Annual Convention of the American Medical Association. The 1949 written examination will be given on October 17, 1949, the closing date for applications being May 1.

THE AMERICAN BOARD OF PEDIATRICS, INC., John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa. The next oral examinations will be given on April 22, 23, and 24, 1949, at Baltimore, Md.

THE AMERICAN BOARD OF PHYSICAL MEDICINE, Robert L. Bennett, M.D., Secretary-Treasurer, 30 N. Michigan Ave., Chicago 2, Ill. The examination period will be immediately prior to the Annual Convention of the American Medical Association, June 4 and 5. Applications must be complete and in the hands of the Secretary-Treasurer three months prior to this date.

THE AMERICAN BOARD OF RADIOLOGY, B. R. Kirklin, M.D., Secretary-Treasurer, Mayo Clinic, Rochester, Minn. *Memorandum on Certification of radiation physicists:* Beginning January 1, 1949, The American Board of Radiology will examine and certify physicists as radiation physicists. Three types of certificates will be granted: (1) Radiological Physics; (2) X-ray and Radium Physics; (3) Medical Nuclear Physics; (2) and (3) are both included in (1).

Each applicant for any one of the certificates in radiation physics will be required to meet the following standards: (a) Satisfactory moral and ethical standing; (b) That he holds himself to be a specialist in the category of physics designated in his application; (c) That he be a citizen of the United States or Canada. Candidates from other countries must be permanent residents of that country and native citizens thereof; (d) That he holds a degree of Bachelor of Arts or its equivalent and has majored in physical science or engineering; (e) That he be a member of the American Physical Society or similar organization; (f) That after graduation from college he has had at least one year postgraduate experience in radiation physics or in a radiation physics laboratory.

(g) Candidates for examination in Radiological Physics in addition to requirements specified in paragraphs (a), (b), (c), (d), (e) and (f) must have had at least one year of experience in association with a Department of Radiology approved by the Board and throughout one of the two years specified must have had experience in medical application of artificial radioactive materials.

Each candidate shall submit with his application personal records of calibrations of one low voltage and one high voltage x-ray apparatus, personal records of one x-ray protection survey and one protection survey for radioactive materials.

(h) Candidates for examination in X-ray and Radium Physics in addition to requirements specified in paragraphs (a), (b), (c), (d), (e) and (f) must have had at least one year of experience in association with a Department of Radiology approved by the Board. With the application he must submit records of personal calibration of one low voltage and one high voltage x-ray apparatus and personal records of one x-ray protection survey and one personal protection survey for radium.

(i) Candidates for examination in Medical Nuclear Physics in addition to requirements specified in paragraphs (a), (b), (c), (d), (e) and (f) must have had one year of experience in physical procedures relative to medical application of radioactive materials.

(j) Applications shall be endorsed by a Diplomate of the American Board of Radiology and a Diplomate in Radiological Physics who have personal knowledge of the experience, training, moral and ethical standing of the applicant and that he is qualified to take an examination.

(k) A fee of \$25.00 shall accompany the application which will be refunded if the application for examination is not accepted.

(l) Applications shall be submitted to the Secretary of The American Board of Radiology. He shall forward them to the Credentials Committee on Radiological Physics to be appointed by the Board, who shall decide about the candidate's fitness to be examined. Those approved for examination shall be informed by the Secretary of the Board when and where to appear.

Examinations will usually be conducted at the time and place of the regular or special meetings of the American Board of Radiology.

Examinations in radiation physics shall be oral, though practical or written examinations may be required. Examinations will be designed to test the candidate's knowledge and his fitness to practice physics in the category for which he applies. Accordingly, the examination may include questions regarding the structure of matter, construction and operation of x-ray apparatus, the use of radiation measuring instruments, determination of radiation quantity and quality, protection from x-rays, radium and artificial radioactive substances, preparation of radioactive applicators,

determination of dosages of x-rays, radium and radioactive substances and other questions relative to the category in which the candidate applies.

Candidates who fail an examination shall not be admitted to another examination until one year has elapsed. They must request reëxamination at least sixty days prior to the next meeting of the Board and pay an additional fee of \$10.00.

A diploma may be revoked if in the opinion of the Board a mis-statement of fact has been made in the application or any other communication to the Board or its representatives, or for expulsion from a scientific society for misconduct. Under such circumstances the diplomas must be returned to the Board and the name of the individual shall be omitted from the Registry of Diplomates.

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#### AMENDMENTS PROPOSED TO THE CONSTITUTION AND BY-LAWS

The Board of Regents of The American College of Physicians on November 7, 1948, formally adopted a resolution recommending the following amendments to the Constitution and By-Laws, to provide for Honorary Fellows.

Constitution, Article IV, to be amended by changing the introductory sentence to read "Members of The American College of Physicians shall be of three classes: (a) Fellows; (b) Masters; and (c) Honorary Fellows."

By adding a new Section to Article IV as follows: "(c). Honorary Fellows. Honorary Fellows shall be internists, members of the medical profession of countries other than the United States or Canada, who on account of personal character, positions of honor and influence, or eminence in the practice of internal medicine or in research, shall be recommended by the Committee on Masterships to the Board of Regents. Honorary Fellows shall not have the right to vote or to hold office."

Article IV, Section (b), shall be amended by reversing the order of the words "influence and honor" to read "honor and influence."

By-Laws, Article VI, the title to be amended to read, "Election of Masters and Honorary Fellows"; also by numbering the first paragraph "(a)", and adding paragraph "(b)". The Committee on Masterships may also present to the Board of Regents nominations for the election of Honorary Fellows. Not more than two Honorary Fellows shall be elected in any calendar year."

These amendments will be presented for action by the Fellows and Masters of the College at the Annual Business Meeting at New York City on March 31, 1949.

## OBITUARIES

## DR. HUGH S. CUMMING

Hugh Smith Cumming, M.D., F.A.C.P., distinguished former Surgeon General of the U. S. Public Health Service, died at his home in Washington, D. C., on December 20, 1948.

Dr. Cumming was born at Hampton, Va., August 17, 1869. He attended the University of Virginia Department of Medicine and received his degree in 1893. The following year he served as house doctor in St. Luke's Hospital, Richmond, and received a second M.D. degree from the University College of Medicine (Richmond). He then obtained a commission as Assistant Surgeon in the U. S. Marine Hospital Service, later designated the U. S. Public Health Service.

During the years before his first appointment as Surgeon General in 1920, Dr. Cumming's outstanding career provided him with an experience in important national and international problems of public health. The subjects on which he became an authority included tropical diseases, quarantine inspection, bubonic plague, pollution of tidal waters, sanitation, industrial medicine and public health administration. His assignments took him to New York, San Francisco, Cape Charles, to Cannes and Yokohama and many other widely separated cities. During World War I, Dr. Cumming served in the Office of the Surgeon General of the Navy, and in 1918 went to France for sanitary studies at camps and ports.

Dr. Cumming served as Surgeon General from 1920 to 1936. Among the accomplishments of his administration are the completion of the national quarantine system, reorganization and expansion of the Service's staff and its hospital facilities, establishment of a national leprosarium and a Division of Mental Hygiene, assignment of medical officers to examine prospective immigrants at American Consulates abroad, development or expansion of research into problems important to industrial and public health, construction of two hospitals for narcotic addicts, and the successful developments which culminated, prior to his retirement, in the Congressional appropriations making possible the construction of the present National Institutes of Health.

Dr. Cumming was director of the Pan American Sanitary Bureau from 1920 to 1947 and contributed to its growth in usefulness. He was also a president of the Office International d'Hygiene and a vice president of the League of Nations Health Section.

Recognition of Dr. Cumming's contributions was not lacking. He was awarded honorary degrees of Sc.D. by the University of Pennsylvania in 1930 and LL.D. by Yale University in 1933, the Hartley Medal of the National Academy of Sciences in 1936, the Gorgas Medal and Prize of the Association of Military Surgeons of the United States, and the William Freeman Snow Award. He was commander of the Legion of Honor of France, and, with Star, of Poland Restored, and had been honored by Peru, Ecuador, Chile, Mexico, Cuba, Colombia and the Dominican Republic.

Dr. Cumming was a former president of the American Public Health and Southern Medical Associations, of the Association of Military Surgeons of the United States, and of the Gorgas Memorial Institute of Tropical and Preventive Medicine, an honorary fellow of the American Colleges of Surgeons and of Dentists and of the Canadian Public Health Association, and a member of the American Medical and Hospital Associations, Alpha Omega Alpha, Phi Beta Kappa, and other societies. Elected to Fellowship in the American College of Physicians in 1923, Dr. Cumming gave it service for many years as a member of its Board of Governors while he was Surgeon General.

## DR. PAUL SCOTT HANSEN

Dr. Paul Hansen was born in Columbus, Ohio, October 16, 1910, and died September 26, 1948, at the Santa Barbara General Hospital, Santa Barbara, Calif., of poliomyelitis.

He received his Bachelor of Science degree from Harvard University in 1931, and then attended Northwestern University Medical School where he received his M.D. degree in 1938.

Dr. Hansen was a diplomate of the National Board of Medical Examiners and the American Board of Internal Medicine; he was a member of the American Medical Association and was elected to associateship in the American College of Physicians during the 1948 San Francisco meeting. He was formerly on the faculties of the University of Pennsylvania School of Medicine and the Yale University School of Medicine. During World War II Dr. Hansen served as a captain with the 15th Evacuation Hospital in Africa, Sicily and Italy. He was separated from the service as a major after 33 months of service overseas. During the time Dr. Hansen practiced in Santa Barbara, he was consultant on blood diseases at the Santa Barbara Clinic, and was affiliated with the Santa Barbara Cottage Hospital and the Santa Barbara General Hospital.

Dr. Hansen was a very fine and able physician, and will be greatly missed by all who knew him.

LELAND HAWKINS, M.D., F.A.C.P.,  
Governor for Southern California

## DR. GEORGE J. KASTLIN

The untimely death of George Jacob Kastlin, M.D., F.A.C.P., on December 31, 1948, at the age of 48, is a tragic loss to his professional colleagues and his many friends. At the time of his death, Dr. Kastlin was Associate Professor of Medicine in the University of Pittsburgh, senior staff physician to the Presbyterian and St. Margaret's Memorial Hospitals, consulting hematologist to St. John's General Hospital, Montefiore Hospital and Pittsburgh Diagnostic Clinic, senior consultant to the Veterans Administration Hospital, Aspinwall, and associate medical director of the Pittsburgh Skin and Cancer Foundation.

Dr. Kastlin was born in Savanna, Ill., July 11, 1900. He received the degree of B.S. from the University of Wisconsin in 1922, and M.D. from the University of Pennsylvania in 1924. He interned at the Mercy Hospital, Pittsburgh, 1924-25, and was a resident in pathology at the Toronto General Hospital, 1925-26. In 1926-27 he held the position of assistant clinical pathologist at the State of Wisconsin General Hospital and instructor in clinical pathology in the University of Wisconsin Medical School. In 1927, he returned to Pittsburgh where he established a wide reputation as a specialist in diseases of the blood and lymph glands.

During the war he served in the Medical Corps, A.U.S., 1942-46, separating with rank of Colonel.

Dr. Kastlin was a member of the Allegheny County Medical Society and the Medical Society of the State of Pennsylvania, and a fellow of the American Medical Association. He was a member of the American Society of Clinical Pathologists, American Association of Pathologists and Bacteriologists, the Clinical-Pathological Society of Pittsburgh, the Toronto Academy of Medicine, and, since 1931, was a fellow of the American College of Physicians.

Dr. Kastlin combined, to an unusual degree, an accurate knowledge of the basic sciences with great clinical intuition, so that he was especially successful in the treatment of those suffering with glandular and hematologic disorders. He was a clear



thinker and a vivid lecturer and took a very active part in symposia and postgraduate sessions. In particular, he made outstanding contributions to the courses in internal medicine given in Pittsburgh by the American College of Physicians.

Above all, George Kastlin was singularly free from petty envy or jealousy. He was kind and generous, and always ready to share his technical facilities and knowledge with his colleagues. He will be sadly missed by a host of friends and admirers.

R. R. SNOWDEN, M.D., F.A.C.P.,  
Governor for Western Pennsylvania

### DR. THEOPHIL KLINGMANN

Theophil Klingmann, M.D., F.A.C.P., of Ann Arbor, Mich., died there on September 19, 1948. Born in that city in 1868, Dr. Klingmann was a graduate of the University of Michigan (Ph.C. and M.D., 1892). He served as pathologist to the Michigan State Hospital for the Insane, 1901-05, and as instructor in neuropsychiatry and demonstrator in neuropathology, University of Michigan Medical School, 1901-18. He undertook postgraduate studies in Leipzig and Berlin, 1906-08; in Vienna, 1910; and in Philadelphia, in 1912. Formerly medical director of Mercywood Psychiatric Hospital, Dr. Klingmann was also chief of the Division of Neuropsychiatry in St. Joseph's Mercy Hospital.

Dr. Klingmann was a past president of the Washtenaw County Medical Society, past vice president of the Detroit Society of Neurology and Psychiatry, a member of the American Psychiatric Association, Association for Research in Nervous and Mental Disease, and a fellow of the American Medical Association. He was one of the early members of the American College of Physicians, having been elected to fellowship in 1919.

### DR. JOHN J. MOREN

John J. Moren, M.D., F.A.C.P., died on October 26, 1948, at the Veterans Administration Hospital, Louisville, Ky., of pleurisy with effusion. He was in his 78th year.

Born in London, Ky., he attended Center College and the University of Kentucky. He had an M.D. degree from the Louisville Medical College in 1894, and an M.D. degree from the Hospital College of Medicine, Louisville, in 1895. He immediately specialized in neurology, taking postgraduate work in Philadelphia, New York, Berlin and London. He was engaged in the practice of medicine in Louisville from 1894 to 1941.

Dr. Moren was a member of the faculty of the University of Louisville School of Medicine for 40 years, and was Clinical Professor of Neurology and Head of the Department of Neurology from 1928 until 1940 when he became emeritus. He served overseas as a Major in the U. S. Army Medical Reserve Corps during World War I. He was President of the Jefferson County Medical Society in 1906, and of the Kentucky State Medical Association in 1915. He had been a fellow of the American College of Physicians since 1917.

Dr. Moren was the epitome of the physician, a kindly, courteous, gentlemanly scholar, throughout his entire lifetime. Up until his death, he constantly kept abreast of new developments in medicine in general as well as in his own particular field. He was a most unusual teacher who succeeded in teaching sound medical principles along with his neurology. His modest seeking after knowledge was an inspiration to generations of medical students who profited by their contact with him in many more ways than simply from the neurology he taught.

WILLIAM K. KELLER, M.D., F.A.C.P.

## DR. ROBERT M. MORRISON

Robert Mehard Morrison, M.D., F.A.C.P., of Youngstown, Ohio, died November 19, 1948. Dr. Morrison was born in Wurtemburgh, Pa., in 1872 and received his medical education at the University of Pittsburgh School of Medicine, from which he received his degree in 1895. For many years a consulting physician and subsequently Chairman of the Board of Youngstown Hospital, Dr. Morrison practiced general medicine with emphasis on internal medicine.

Dr. Morrison was a member of the Mahoning County, Ohio State and American Medical Associations. He became a fellow of the American College of Physicians and a member of The American Congress on Internal Medicine in 1920.

## DR. JOSEPH H. BRYAN

Joseph Harker Bryan, M.D., of Asbury Park, N. J., died October 21, 1948.

Dr. Bryan was born in Newark, N. J., December 15, 1865. He received his Bachelor of Arts degree from New York University in 1886 and his Medical Degree from the New York Homeopathic Medical College and Flower Hospital in 1890. He was long active in the medical profession of New Jersey, serving as a member of the medical staff of Fitkin Memorial Hospital, in Neptune, and as a member and president of the New Jersey State Board of Medical Examiners. He was also a member of the American Institute of Homeopathy and a former president of the New Jersey State Homeopathic Society.

Dr. Bryan had been a Fellow of the American College of Physicians since 1931.

## DR. IRVIN REGINALD FOX

Dr. Irvin Reginald Fox was born January 25, 1891, in Oregon City, Ore., and died September 21, 1948, at his home in Eugene, Ore.

Dr. Fox received his M.D. degree from the University of Oregon Medical School in 1921, and, following this, served an internship at Emanuel Hospital in Portland. He entered practice in Eugene and early limited his practice to internal medicine. He soon became a leader in medicine in that city and, at the time of his death, was recognized widely for his ability, his scientific interest, his energy and enthusiasm for the advancement of medicine. This, coupled with his great sincerity, endeared him to his patients and earned for him the respect of his colleagues throughout the state. He was the author of a number of medical articles and was frequent in his attendance at the meetings of the many societies to which he belonged.

During his active career, he was long a member of the Eugene City Board of Health and the Oregon State Board of Medical Examiners. While a member of the staffs of the Eugene and Sacred Heart Hospitals, he worked consistently for the improvement of the standards of medical care in these institutions, and at the time of his death was a member of the governing board of the Sacred Heart Hospital. His influence was important in the development of the high standards at the hospitals where he worked. He was instrumental in organizing a Journal Club which continues to be very active at the present.

Dr. Fox was a fellow of the American Medical Association and of the American College of Chest Physicians, a member of the Oregon State Medical Society, the American Diabetic Society and the North Pacific Society of Internal Medicine. He became a Fellow of the American College of Physicians in 1941.

He enjoyed a very active and extensive practice in his community. The community, his patients and his host of medical friends throughout the Northwest mourn his untimely death and all realize they have lost a great and good friend and doctor.

HOWARD P. LEWIS, M.D., F.A.C.P.,

Governor for Oregon

# PROGRAM

## THE AMERICAN COLLEGE OF PHYSICIANS

Thirtieth Annual Session

NEW YORK, N. Y.

March 28–April 1, 1949

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### GENERAL SESSIONS AND LECTURES

Walter W. Palmer, New York, N. Y., President

### GENERAL CHAIRMAN

Franklin M. Hanger, New York, N. Y.

### COMMITTEE ON ARRANGEMENTS

Franklin M. Hanger, Chairman

Ralph H. Boots  
Alexander B. Gutman  
Carl Muschenheim

Howard A. Rusk  
Theodore B. Russell  
Harold J. Stewart

Mrs. Edgar Stillman

### COMMITTEE ON AUDITORIUM

Theodore B. Russell, Chairman

Henry Horn  
Albert C. Santy

Frank E. Smith, Jr.  
Terence Lloyd Tyson

Byard Williams

### COMMITTEE ON CLINICS

Harold J. Stewart, Chairman

David P. Barr, New York Hospital  
J. Hamilton Crawford, Long Island College Hospital  
Clarence E. de la Chapelle, Lenox Hill Hospital  
William Dock, Kings County Hospital  
Waldo B. Farnum, St. Luke's Hospital  
Alexander B. Gutman, Goldwater Memorial Hospital, First Division (Columbia University)  
Louis Leiter, Montefiore Hospital for Chronic Diseases  
Leo Loewe, Jewish Hospital, Brooklyn  
Walter G. Lough, New York University-Bellevue Medical Center, Post-Graduate Medical School and University Hospital  
Edwin P. Maynard, Jr., Brooklyn Hospital  
Thomas H. McGavack, Flower and Fifth Avenue Hospitals  
Rulon W. Rawson, Memorial Hospital  
Dickinson W. Richards, Jr., Bellevue Hospital, First (Columbia) Medical Division  
Thomas M. Rivers, Hospital of the Rockefeller Institute for Medical Research

Howard F. Shattuck, Roosevelt Hospital  
 J. James Smith, Bellevue Hospital, Second (Cornell) Medical Division  
 Isidore Snapper, Mount Sinai Hospital  
 J. Murray Steele, Goldwater Memorial Hospital, Third Division (New York University)  
 Bernard Straus, Veterans Administration Hospital, Bronx  
 William S. Tillett, Bellevue Hospital, Third (New York University) Medical Division  
 Randolph West, Presbyterian Hospital

### COMMITTEE ON ENTERTAINMENT

Ralph H. Boots, Chairman

George C. Andrews, Jr.	Oswald R. Jones
Norton S. Brown	Bernard S. Oppenheimer
Russell L. Cecil	Frank H. Peters
John Staige Davis, Jr.	Howard F. Shattuck
Richard H. Freyberg	Edgar Stillman
Irving S. Wright	

### COMMITTEE ON HOTELS AND TRANSPORTATION

Carl Muschenheim, Chairman

Gurney Taylor	David Ulmar
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### COMMITTEE ON PANEL DISCUSSIONS

Alexander B. Gutman, Chairman

John H. Keating	Ephraim Shorr
Henry G. Kunkel	Louis J. Soffer
Louis Leiter	J. Murray Steele
Edward C. Reifenshtein, Jr.	Bernard Straus

### COMMITTEE ON PUBLICITY

Howard A. Rusk, Chairman

Arthur J. Antenucci	Howard G. Bruenn
Frederick R. Bailey	Charles K. Friedberg

### COMMITTEE ON TECHNICAL EXHIBITS

George Morris Piersol, Chairman

Thomas Klein	Charles C. Wolfert
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### COMMITTEE ON WOMEN'S ENTERTAINMENT

Mrs. Edgar Stillman, Chairman

Mrs. George Baehr	Mrs. G. Jarvis Coffin
Mrs. Alvan L. Barach	Mrs. Jean A. Curran, Sr.
Mrs. Louis F. Bishop, Jr.	Mrs. A. L. Garbat
Mrs. Ralph H. Boots	Mrs. Franklin M. Hanger
Mrs. Russell L. Cecil	Mrs. Albert R. Lamb, Sr.
Mrs. Henry T. Chickering	Mrs. Robert L. Levy

Mrs. Edwin P. Maynard, Jr.  
 Mrs. Currier McEwen  
 Mrs. James Alexander Miller  
 Mrs. Walter W. Palmer  
 Mrs. Harold E. B. Pardee  
 Mrs. Cornelius P. Rhoads

Mrs. Thomas M. Rivers  
 Mrs. Howard F. Shattuck  
 Mrs. Frank E. Smith, Jr.  
 Mrs. Louis J. Soffer  
 Mrs. Gurney Taylor  
 Mrs. Kenneth Taylor

## INVITATION .

As one of the world's greatest medical centers, New York extends its welcome to the Fellows, Associates and friends of The American College of Physicians. Those that reside in the Greater New York area, the New York Academy of Medicine, the County Medical Societies, the local hospitals and medical centers and the Department of Health of the City of New York, are anxious that your visit to New York be not only as professionally profitable but as comfortable and entertaining as possible. Since the College was last our guest ten years ago, there have been many changes in our city. New and great medical institutions and services such as the Public Health Research Institute, the Sloan-Kettering Institute for Cancer Research, the Montefiore and Department of Hospitals' home care programs, the United Medical Service and Health Insurance Plan of New York, the New York University-Bellevue Medical Center, the Hospital Council of Greater New York have been started. Our other internationally known hospitals, clinics, foundations and services, and our five medical schools—Columbia University College of Physicians and Surgeons, New York University College of Medicine, Cornell University Medical College, Long Island College of Medicine and New York Medical College, Flower and Fifth Avenue Hospitals—have continued their leadership. They too are anxious that you have every opportunity while in New York to share their advances with them.

Our New York Academy of Medicine, which observed its centennial last year, invites you to visit its building at 2 E. 103rd Street and to make use, if you desire, of its medical library, the second largest collection of medical literature in the United States. Center for the activities of practicing physicians and surgeons of New York, the Academy of Medicine is headquarters for many local and national medical groups.

As New York is also one of the world's greatest centers of culture, entertainment, commerce and industry, we welcome you to those aspects of New York and bid you share in that which may not be available in your own community. The shops along Fifth Avenue, Times Square at night, the view from the Empire State Building, the Metropolitan Museum of Art, Rockefeller Foundation, the intimate restaurants serving foreign foods, Chinatown, the big brassy night clubs, the American Museum of Natural History, the theaters and the opera, the oratory at Union Square, the carriage rides in Central Park, The Little Church Around the Corner, the craft shops in Greenwich Village—these are ours, they are the things that make New York, the New York of O. Henry, Mark Hellinger, and Damon Runyon. This week of our Meeting, they are yours also. We hope you enjoy them as much as we.

FATHER KNICKERBOCKER

## GENERAL INFORMATION

### GENERAL HEADQUARTERS

Waldorf-Astoria Hotel

Park Avenue and 50th Street

Registration headquarters, the information bureau, technical exhibits, general sessions, morning lectures, panel discussions, certain selected clinics and clinico-patho-

logical conferences, meetings of committees, of the Board of Regents, and of the Board of Governors. The Annual Convocation and the Annual Banquet will take place in the Grand Ballroom of this Hotel.

### HOTEL ACCOMMODATIONS

A fully adequate number of first-class guest rooms has been reserved in close proximity to the Waldorf-Astoria Hotel, and a Housing Bureau, working through the Committee on Hotels and Transportation, has been set up at the New York Convention Bureau, 500 Park Avenue, New York 22, N. Y. Applications for rooms should be made to this Bureau, preferably on the official form provided by the College, but in the absence of the form, the Housing Bureau will handle letters of application, provided the applicant identifies himself with the College and its Annual Session. It is requested that five choices of hotels be indicated, and that a reasonable range of rates be shown. Whenever possible arrangements should be made for occupancy of rooms accommodating two persons. Confirmation from the hotel where the reservation has been made will be mailed to each applicant. If, after making reservations, the applicant finds it impossible to attend, he is requested to notify the Housing Bureau promptly so that his accommodations may be made available to another physician.

A very limited number of rooms were made available at the Waldorf-Astoria Hotel, but adequate and satisfactory accommodations are available nearby.

### LIST OF OFFICIAL HOTELS

Hotel	Type of Room and Rate *
WALDORF-ASTORIA	100 doubles ..... \$10.00 to \$16.00
Park Avenue and 50th Street	25 suites ..... 18.00 to 32.00
BELMONT-PLAZA	90 doubles ..... \$ 6.50 to \$ 9.50
Lexington Avenue and 49th Street	5 suites ..... 12.00 to 15.00
ABBEY	12 singles ..... \$ 3.75 to \$ 5.00
149 W. 51st Street	38 doubles ..... 6.00 to 8.00
AMBASSADOR	10 doubles ..... \$ 9.00 to \$14.00
Park Avenue and 51st Street	5 suites ..... 16.00 to 25.00
BARCLAY	50 doubles ..... \$11.00 to \$13.00
111 E. 48th Street	
BILTMORE	100 doubles ..... \$10.00 to \$17.00
Madison Avenue and 43d Street	
COMMODORE	70 singles or doubles
Lexington Avenue and 42nd Street	singles ..... \$ 5.50 to \$ 7.50
	doubles ..... 8.50 to 10.00
	200 twins ..... 11.50
	15 combinations ..... 13.00
DELMONICO	6 singles ..... \$10.00
502 Park Avenue	10 suites ..... 18.00 to \$22.00
GOTHAM	10 doubles ..... \$ 9.00 to \$14.00
Fifth Avenue and 55th Street	
NEW WESTON	30 doubles ..... \$ 8.00 to \$10.00
34 E. 50th Street	5 suites ..... 12.00 to 20.00
PARK CENTRAL	50 doubles ..... \$ 8.50 to \$10.00
Seventh Avenue and 56th Street	75 suites ..... 10.00 to 14.00
PICCADILLY	75 doubles ..... \$ 6.00 to \$ 8.00
227 W. 45th Street	

PLAZA	10 singles .....	\$ 9.00 to \$12.00
Fifth Avenue and 59th Street	40 doubles .....	10.00 to 18.00
ROOSEVELT	50 singles .....	\$ 6.50 to \$10.00
Madison Avenue and 45th Street	350 doubles .....	10.50 to 15.00
ST. REGIS	3 singles .....	\$ 8.00 to \$10.00
Fifth Avenue and 55th Street	6 doubles .....	12.00 to 14.75
SHELTON	25 singles .....	\$ 4.50 to \$ 6.50
Lexington Avenue and 49th Street	75 doubles .....	6.50 to 8.00
SHERATON	10 doubles .....	\$ 8.00 to \$10.00
303 Lexington Avenue	10 suites .....	10.00 to 12.50
Taft	50 singles .....	\$ 4.00 to \$ 7.00
Seventh Avenue and 50th Street	150 doubles .....	6.50 to 9.00
VANDERBILT (10 minutes by cab)	10 singles .....	\$ 4.50 to \$ 7.00
Park Avenue and 34th Street	15 doubles .....	8.00 to 10.00
VICTORIA	10 singles .....	\$ 5.00
Seventh Avenue and 51st Street	65 doubles .....	7.00 to \$ 9.00
WARWICK	75 doubles .....	\$12.00
65 W. 54th Street	25 suites .....	20.00
WENTWORTH	20 doubles .....	\$ 7.00 to \$ 8.00
59 W. 46th Street	15 suites .....	12.00 to 14.00
WINTHROP	6 doubles .....	\$ 7.00 to \$ 9.00
Lexington Avenue and 47th Street		

\* Subject to 5 per cent New York City Sales Tax.

### Who May Register—

- (a) All members of The American College of Physicians in good standing for 1949.
- (b) All newly elected members.
- (c) Graduate medical students pursuing courses at medical schools in Greater New York, without registration fee, upon presentation of matriculation cards or other evidence of registration at these institutions; admission to exhibits, general sessions and morning lectures.
- (d) Members of the staff, including interns, of the hospitals participating in the program, without registration fee, upon presentation of proper identification; admission to exhibits, general sessions and morning lectures.
- (e) Members of the Medical Corps of the Army, Navy, Public Health Service and Veterans Administration, either of the United States or Canada, without registration fee, upon presentation of proper credentials.
- (f) Qualified physicians who may wish to attend this Session as visitors or in company with physicians who are members of the College; such physicians shall pay a registration fee of \$15.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

**Registration Bureau**—While official registration will start on Monday morning, March 28, advance registration of members and exhibitors will be provided for on Sunday, March 27, from 2:30 to 5:00 in the afternoon. The Registration Bureau, located in the Silver Corridor, Ballroom Floor, will be open through the week from 8:30 A.M. to 5:45 P.M.

Registration Blanks for all Clinics, Clinico-Pathological Conferences and Panel Discussions will be sent with the individual program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Board for special announcements will be located near the Registration Bureau at the Waldorf-Astoria.

Transportation—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the Meeting.

The General Business Meeting of the College will be held from 2:00 to 2:40 P.M., Thursday, March 31, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the annual reports of the Secretary-General, Executive Secretary and Treasurer, and the presentation of certain amendments to the Constitution and By-Laws. The President-Elect, Dr. Reginald Fitz, Boston, Mass., will be inducted into office.

Board and Committee Meetings—All meetings will be held at the Waldorf-Astoria. Special meetings will be announced and posted.

A Dinner Meeting of the Board of Regents and of the Board of Governors will be held in the Jansen Suite, Fourth Floor of the Waldorf-Astoria, Sunday, March 27, at 7:00 P.M.

#### Committee on Credentials

Saturday, March 26, 10:00 A.M., Carpenter Salon, Fourth Floor

#### Committee on Credentials and Executive Committee

Saturday, March 26, 2:30 P.M., Carpenter Salon, Fourth Floor

#### Committee on Fellowships and Awards

Sunday, March 27, 10:00 A.M., Carpenter Salon, Fourth Floor

#### Committee on Educational Policy and Advisory Committee on Postgraduate Courses

Sunday, March 27, 11:00 A.M., Carpenter Salon, Fourth Floor

#### Joint Meeting: Board of Regents and Board of Governors

Sunday, March 27, 2:00 P.M., Jansen Suite, Fourth Floor

#### Committee on Nominations

Monday, March 28, 10:00 A.M., Carpenter Suite, Fourth Floor

#### Committee on Finance

Monday, March 28, 10:00 A.M., Chinese Room, Fourth Floor

#### Committee on Public Relations

Monday, March 28, 11:00 A.M., Carpenter Salon, Fourth Floor

#### Board of Regents

Tuesday, March 29, 12:00 M., Carpenter Salon, Fourth Floor \*

Friday, April 1, 12:00 M., Carpenter Salon, Fourth Floor \*



**Board of Governors**

Wednesday, March 30, 12:00 M., Carpenter Salon, Fourth Floor\*

**SPECIAL FEATURES**

**Special Trains**—No official arrangements have been concluded for complete special trains, but, in numerous localities in the West and Far West, the College Governors have sponsored special cars on certain trains to New York and return. Members are advised to consult the Governors for their states on provisions concerning special cars.

**Post-Convention Cruise to Bermuda**—A special post-convention cruise to Bermuda has been arranged at the request of members and their families and friends. The cruise will be under the direction of Mr. Leon V. Arnold, Travel Consultant, 36 Washington Square West, New York 11, N. Y. The number of accommodations is somewhat limited and members are urged to communicate immediately with Mr. Arnold to secure plans of the ship, to select staterooms and to complete reservations.

The Queen of Bermuda will leave New York City at 3:00 P.M., Monday, April 4, arriving at Hamilton, Bermuda, 7:00 A.M., April 6. Guests will be accommodated at the Hotel Bermudiana and at the Hotel Princess. Motor or carriage drives to St. George's, Somerset, Gibb's Hill or Spanish Point will be arranged; time available to visit the celebrated caves and coral underseas gardens; to shop; golf; to follow the camera or other diversions. Party will cast off from Hamilton at 3:00 P.M., April 8, arriving back in New York at 9:00 A.M., April 10.

**Grand Reception, March 28, 5:00 to 7:00 P.M.**—The combined men's and women's Committees on Entertainment have arranged a Grand Reception and Cocktail Party on Monday evening, 5:00 to 7:00 P.M., in the Starlight Roof of the Waldorf-Astoria. This will be a feature of the entertainment program, an opportunity for all in attendance to assemble for an hour or two of sociability and for renewing acquaintanceships and seeing "Who's Here." Tickets available at the Registration Bureau in the Silver Corridor and at the Women's Registration Headquarters, Fourth Floor of the Waldorf-Astoria. Price, \$3.00.

**The Annual Convocation and the President's Reception, Wednesday, March 30**—The Annual Convocation of the College will be held at 8:30 P.M., March 30, in the Grand Ballroom of the Waldorf-Astoria. All members of the College and their families, and those of the public who are interested, are cordially invited. All physicians elected Fellows of the College since the 1948 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors and new Fellows to be inducted are requested to assemble in Le Perroquet Suite, Fourth Floor, at 7:45 P.M., preparatory to the formation of the procession. They will be conducted to their seats by the Marshal of the Convocation, Dr. T. Grier Miller, promptly at 8:30 o'clock. It is suggested that all appear in evening clothes.

The Convocation ceremony will include the President's address and a Convocational Oration by Henry Allen Moe, Secretary General, The John Simon Guggenheim Memorial Foundation, New York, N. Y. The John Phillips Memorial Medal for 1949, the James D. Bruce Memorial Medal for 1949 and the Alfred Stengel Diploma for 1949 will be awarded. Recipients of Research Fellowships of the College for 1949 will be announced, and Masterships will be conferred upon four outstanding Fellows of the College. The new Fellows to be inducted will be presented by the Secretary General, Dr. George Morris Piersol, and, after subscribing to the Fellowship Pledge, will be inducted by the President. Following the Convocation, after a brief inter-

\* Buffet Luncheon served.

mission during which guests will retire to the Foyer while the Ballroom is cleared, the President's Reception and Dance will take place in the Ballroom. All members and guests are requested to pass along the receiving line at the Reception.

**The Annual Banquet**—A "Dutch Treat" Cocktail Party has been arranged from 7:00 to 8:00 P.M. in the Sert Room, Office Floor, of the Waldorf-Astoria Hotel. All are encouraged to joint in this general preprandium instead of having numerous and scattered private parties. The Annual Banquet will be held in the Grand Ballroom of the Waldorf-Astoria at 8:00 P.M., Thursday, March 31. Some unusual musical features are planned and the speaker will be an individual of national or international reputation whose name and title will be announced later. The Annual Banquet should be a sparkling and delightful occasion at which every member, his guests and friends should be present. Table reservations for groups may be arranged. Tickets should be obtained at the Registration Bureau by Wednesday afternoon, March 30, so that adequate preparations can be consummated.

### Other General Entertainment Features

**Monday Night Theater Parties, March 28**—The Entertainment Committee will publish a list of the plays appearing at that time, with prices, and arrangements have been made whereby members of the College may apply for tickets in advance to Sullivan's Theater Ticket Office, Waldorf-Astoria Hotel. A service charge of \$.75 for each ticket will be made by the agency. It is suggested that members indicate first, second and third choice of plays.

**Radio City Music Hall, Tuesday, March 29**—Nine hundred and forty-four reserved seats are available in the Mezzanine. The stage show starts about 9:00 P.M. Ticket holders should arrive between 8:30 P.M. and 9:00 P.M. Price of seats, \$2.40.

**Entertainment of Visiting Women**—The Women's Entertainment Committee has prepared the following program to welcome to New York the wives of the members of the American College of Physicians, hoping that they will enjoy their visit and take away with them pleasant memories of their stay. Those arriving early may register Sunday afternoon, March 27, from 2:30 to 5:00 P.M. in the Assembly Suite on the Fourth Floor of the Waldorf-Astoria. Registration will continue Monday through Thursday from 9:00 A.M. to 4:00 P.M.

Certain of the entertainment features are limited in accommodations and, therefore, early registration for each event is essential.

### Monday, March 28, 1949

9:00 A.M. to 4:00 P.M., Registration, Room 4M, Assembly Suite, Fourth Floor, Waldorf-Astoria.

5:00 P.M. to 7:00 P.M., Grand Reception and Cocktail Party for members and their wives, Starlight Roof. Tickets, \$3.00.

Evening: Free.

### Tuesday, March 29, 1949

**Morning: 10:00 A.M.** Trip to United Nations, Lake Success. Tour, \$2.00.

**Afternoon: 2:00 P.M. to 4:00 P.M.** Tour of downtown Manhattan. Buses leave from and return to 49th Street entrance, Waldorf-Astoria. \$2.00.

Trips to the Planetarium, Good Housekeeping Institute (model kitchens, laundries, beauty clinics, etc.), New York Telephone Company and various broadcasts have also been arranged. Information and tickets will be available at the Women's Registration Desk.

4:30 P.M. to 6:30 P.M. Reception Tea in the Cosmopolitan Club, 129 E. 65th Street, as guests of the Women's Committee.

Evening: 9:00 P.M. Reserved seats for regular performance at Radio City Music Hall. Tickets, \$2.40.

### Wednesday, March 30, 1949

Morning: Free.

Afternoon: 12:30 P.M. to 2:30 P.M. Luncheon and "Suddenly It's Spring" Fashion Show, arranged by Lord and Taylor. Starlight Roof, Waldorf-Astoria. Tickets, \$5.00.

Evening: 8:30 P.M. Convocation, followed by President's Reception and Dance, Ballroom, Waldorf-Astoria.

### Thursday, March 31, 1949

Morning: 10:00 A.M. Trip to the United Nations, Lake Success. Guests may return before or after luncheon in the United Nations cafeteria. Tour, \$2.00.

As on Tuesday, trips to the Good Housekeeping Institute, New York Telephone Company and various broadcasts have been arranged. Information and tickets will be available at the Women's Registration Desk in Room 4M, Assembly Suite, Waldorf-Astoria.

Afternoon: Free.

Evening: 7:00 P.M. to 8:00 P.M. "Dutch Treat" Cocktail Party, Sert Room, Waldorf-Astoria. 8:00 P.M. Annual Banquet of the College, Ballroom, Waldorf-Astoria.

Lists of restaurants, shops, beauty parlors, moving picture houses and theaters will be available, specially prepared by the Women's Committee for the use of the College guests. The Committee will also be glad to provide suggestions and information for individual trips to such places of interest as antique shops, art galleries, auction rooms, churches, Empire State Building Observatory, French Lines, historical landmarks, Macy's behind-the-scenes, museums, Waldorf behind-the-scenes, zoos and botanical gardens.

**For the Children**—Trips to the zoo, CBS children's programs, Museum of Science and Industry, Museum of the City of New York, etc., can be arranged. Chaperones and sitters available through the Registration Committee at \$1.00 an hour.

A Women's Reservation Card will accompany the formal program of the Annual Session to be distributed to every member of the College. It is urgently requested that the men see that these cards are promptly handed to their wives so that tentative reservations may be made early by mail.

### SPECIAL PROGRAM

#### SILVER HILL FOUNDATION FOR THE TREATMENT OF THE PSYCHONEUROSES

New Canaan, Conn.

Saturday, April 2, 1949, 10:30 A.M.-12:30 P.M.

New Canaan is forty miles from New York. Seventy-five members are cordially invited to attend as guests of the Foundation. Buses will leave the Waldorf-Astoria

at 9:00 A.M. The Clinic will be from 10:30 A.M. to 12:30 P.M.; luncheon at 1:00 P.M.. Buses will depart for return to New York at 2:30 P.M.

### PROGRAM

Auditorium

(Capacity, 75)

William B. Terhune, presiding

Lecture Clinic on Brief, Intensive, Flexible Methods of Psychotherapy

1. Basic Principles of Brief, Practical Psychotherapy.  
William B. Terhune.
2. Description of Reëducational Methods and Applicability.  
Franklin S. DuBois.
3. Presentation of Case History and Discussion of Practical Methods of Treatment.  
Robert B. Hiden.

### THE TECHNICAL EXHIBIT

The Technical Exhibit will be located on the Ballroom Floor of the Waldorf-Astoria and will practically surround the Ballroom, since it will be conducted in all of the adjoining halls on that floor. The Committee on Exhibits of the College maintains highest possible standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation; irrelevant products are eliminated, and only firms which present a group of approved products of scientific interest to the internist and allied specialists may exhibit.

The exhibitor's aim is to announce new products and to present new and interesting information to members and guests of the College. Likewise, many exhibitors take advantage of this opportunity to give aid and service directions to members who have previously purchased their products. Furthermore, this Exhibit provides the only convenient and direct method of contacting, personally, members of the College.

Members and guests of the College are encouraged to accord the exhibitors courteous and interested attention, thus recognizing their contributions to the Meeting and the effort that they make and the expense to which they go in building superior displays and furnishing, freely, valuable information.

The Exhibits will be open from 8:30 A.M. to 5:45 P.M. daily from Monday through Thursday, and from 8:30 A.M. to 2:45 P.M. on Friday. Special intermissions will be arranged, providing additional time for the inspection of exhibits.

### 1949 EXHIBITORS

Abbott Laboratories, North Chicago, Ill.  
 American Hospital Supply Corporation, Evanston, Ill.  
 Ames Company, Inc., Elkhart, Ind.  
 Appleton-Century-Crofts, Inc., New York, N. Y.  
 Armour Laboratories, The, Chicago, Ill.  
 Association of American University Presses  
 Ayerst, McKenna & Harrison, Limited, New York, N. Y.

Baum Co., Inc., W. A. New York, N. Y.  
Becton, Dickinson & Co., Rutherford, N. J.  
Billhuber-Knoll Corp., Orange, N. J.  
Blakiston Company, The, Philadelphia, Pa.  
Bristol Laboratories, Inc., Syracuse, N. Y.  
Burdick Corporation, The, Milton, Wis.  
Burrroughs Wellcome & Co. (U. S. A.) Inc., Tuckahoe, N. Y.  
Burton Manufacturing Company, Chicago, Ill.

Cambridge Instrument Co., Inc., New York, N. Y.  
Cameron Surgical Specialty Company, Chicago, Ill., and New York, N. Y.  
Carnation Company, Los Angeles, Calif.  
Ciba Pharmaceutical Products, Inc., Summit, N. J.  
Collins, Inc., Warren E., Boston, Mass.  
Commercial Solvents Corporation, New York, N. Y.  
Coreco Research Corporation, New York, N. Y.  
Cream of Wheat Corporation, The, Minneapolis, Minn.

Davies, Rose & Company, Limited, Boston, Mass.  
Davis Company, F. A., Philadelphia, Pa.  
Denver Chemical Mfg. Co., Inc., The, New York, N. Y.  
Devereux Schools, Devon, Pa., and Santa Barbara, Calif.  
Dietene Company, The, Minneapolis, Minn.  
Doak Company, Inc., Cleveland, Ohio  
Doho Chemical Corporation, The, New York, N. Y.

E & J Manufacturing Company, Glendale, Calif.  
Edgerly, Patricia, The New York Medical Exchange  
Electro-Physical Laboratories, Inc., New York, N. Y.

Fleet Co., Inc., C. B., Lynchburg, Va.  
Flint, Eaton & Company, Decatur, Ill.

General Electric X-Ray Corporation, Milwaukee, Wis.  
Gerber Products Company, Fremont, Mich.  
Gradwohl Laboratories, St. Louis, Mo.  
Grune & Stratton, Inc., New York, N. Y.

Harrower Laboratory, Inc., The, Glendale, Calif.  
Heinz Company, H. J., Pittsburgh, Pa.  
Hoeber, Inc., Paul B., New York, N. Y.  
Hoffmann-La Roche, Inc., Nutley, N. J.  
Hollister-Stier Laboratories, Spokane, Wash., Wilkinsburg, Pa., and Los Angeles, Calif.  
Horn Company, William S., Fort Worth, Tex.

International Vitamin Division, Ives-Cameron Company, Inc., New York, N. Y.  
Iodine Educational Bureau, Inc., New York, N. Y.

Jones Metabolism Equipment Co., Chicago, Ill.  
"Junket" Brand Foods, Division of Chr. Hansen's Laboratory, Little Falls, N. Y.

Kalak Water Co. of New York, Inc., New York, N. Y.  
Kelley-Koett Manufacturing Co., The, Covington, Ky.  
Kellogg Company, Battle Creek, Mich.  
Knox Gelatine Co., Inc., Chas. B., Johnstown, N. Y.

- LaMotte Chemical Products Company, Baltimore, Md.  
Larson, Burneice, The Medical Bureau, Chicago, Ill.  
Lea & Febiger, Philadelphia, Pa.  
Lederle Laboratories Division, American Cyanamid Company, New York, N. Y.  
Lilly and Company, Eli, Indianapolis, Ind.  
Lippincott Company, J. B., Philadelphia, Pa.
- Macmillan Company, The, New York, N. Y.  
Maltine Company, The, Morris Plains, N. J.  
McNeil Laboratories, Inc., Philadelphia, Pa.  
Mead Johnson & Company, Evansville, Ind.  
Medical Bureau, The, Chicago, Ill.  
Medical Case History Bureau, New York, N. Y.  
Medical Film Guild, New York, N. Y.  
Merck & Co., Inc., Rahway, N. J.  
Merrell Company, The Wm. S., Cincinnati, Ohio  
Mosby Company, The C. V., St. Louis, Mo.
- Nelson & Sons, Thomas, New York, N. Y.  
New York Medical Exchange, The, New York, N. Y.
- Oxford University Press, Inc., New York, N. Y.
- Parke, Davis & Company, Detroit, Mich.  
Patch Company, The E. L., Boston, Mass.  
Picker X-Ray Corporation, New York, N. Y.  
Procter & Gamble Company, The, Cincinnati, Ohio
- Reed & Carnrick, Jersey City, N. J.
- Sanborn Company, Cambridge, Mass.  
Sandoz Chemical Works, Inc., New York, N. Y.  
Saunders Company, W. B., Philadelphia, Pa.  
Schenley Laboratories, Inc., New York, N. Y.  
Schering Corporation, Bloomfield, N. J.  
Sharp & Dohme, Inc., Philadelphia, Pa.  
Smith, Kline & French Laboratories, Philadelphia, Pa.  
Squibb & Sons, E. R., New York, N. Y.
- Technicon Cardiograph Corp., New York, N. Y.
- U. M. A. Inc., New York, N. Y.  
Upjohn Company, The, Kalamazoo, Mich.  
U. S. Vitamin Corporation, New York, N. Y.
- Varick Pharmacal Co., Inc., New York, N. Y.
- Wallace & Tiernan Products, Inc., Belleville, N. J.  
Warren-Teed Products Company, The, Columbus, Ohio  
Westwood Pharmaceuticals, Division of Foster-Milburn Company, Buffalo, N. Y.  
White Laboratories, Inc., Newark, N. J.  
Williams & Wilkins Company, The, Baltimore, Md.  
Winthrop-Stearns Inc., New York, N. Y.  
Woodward Medical Personnel Bureau, Chicago, Ill.  
Wyeth Incorporated, Philadelphia, Pa.
- Year Book Publishers, Inc., The, Chicago, Ill.

## GENERAL OUTLINE OF NEW YORK SESSION

Hotel events are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	March 28	March 29	March 30	March 31	April 1
9:15 A.M. to 11:30 A.M.	Morning free. Registration, Exhibits, etc.	Hospital Clinics*	Morning Lectures† (9:30-11:30)	Hospital Clinics*	Morning Lectures† (9:30-11:30)
12:00 M. to 1:15 P.M.		Panel Discussions	Panel Discussions	Panel Discussions	Panel Discussions
1:15 P.M. to 2:00 P.M.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2:00 P.M. to 5:00 P.M.	1st General Session	2nd General Session	3rd General Session	Annual Business Meeting 4th General Session	5th General Session
5:00 P.M. to 7:00 P.M.	Grand Reception (Starlight Roof)				
8:00 P.M. to 11:00 P.M.			Convocation, Followed By President's Reception	Annual Banquet	

\* A few clinics and clinical-pathological conferences will be held in the hotel.

† Two simultaneous series.

Note: Exhibits will be open Monday through Thursday from 8:30 A.M. to 5:45 P.M.; on Friday, from 8:30 A.M. to 2:45 P.M.

**GENERAL SESSIONS PROGRAM**

Grand Ballroom, Waldorf-Astoria Hotel

**FIRST GENERAL SESSION**

Monday Afternoon, March 28, 1949

General Chairman, Franklin M. Hanger, F.A.C.P., presiding

P.M.

**2:00 Addresses of Welcome:**

The Honorable WILLIAM O'DWYER, Mayor of New York City.

WILLARD C. RAPPLEYE, F.A.C.P., Dean, Columbia University College of Physicians and Surgeons.

WILLIAM B. RAWLS, F.A.C.P., President, New York County Medical Society.

LEO F. SIMPSON, F.A.C.S., President, The Medical Society of the State of New York.

BENJAMIN P. WATSON, F.R.C.S., F.A.C.S., President, New York Academy of Medicine.

**Response to Addresses of Welcome:**

WALTER W. PALMER, F.A.C.P., President, The American College of Physicians.

President Walter W. Palmer, F.A.C.P., presiding

**2:30 The James D. Bruce Lecture on Preventive Medicine: The Hospital as a Center of Preventive Medicine.**

STANHOPE BAYNE-JONES (by invitation), President of the Joint Administrative Board, The New York Hospital-Cornell College Association, New York, N. Y.

**3:15 INTERMISSION.****3:35 The Diagnosis and Management of Atypical or Virus Pneumonia.**

JOHN H. DINGLE (by invitation), Elizabeth Severance Prentiss Professor of Preventive Medicine, and Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

**3:55 Immunologic Types of Blastomycosis.**

DAVID T. SMITH, F.A.C.P., Professor of Bacteriology and Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C.

**4:15 Treatment of Syphilis.**

J. EARLE MOORE (by invitation), Associate Professor of Medicine, Johns Hopkins University School of Medicine; Adjunct Professor of Public Health Administration, Johns Hopkins University School of Hygiene and Public Health; Baltimore, Md.

**4:35 Prefrontal Operations for the Treatment of Mental Illnesses.**

J. LAWRENCE POOL (by invitation), Professor of Neurological Surgery, Columbia University College of Physicians and Surgeons; Director of the Service of Neurological Surgery, Neurological Institute; New York, N. Y.

**4:55 ADJOURNMENT.**



**SECOND GENERAL SESSION****Grand Ballroom, Waldorf-Astoria Hotel****Tuesday Afternoon, March 29, 1949****Presiding Officer****Reginald Fitz, F.A.C.P., Boston, Mass.****P.M.****2:00 Dietary Invalidism.****HENRY J. JOHN, F.A.C.P., Physician, Lakeside and St. Luke's Hospitals, Cleveland, Ohio.****2:50 Researches in Coronary Heart Diseases.****PAUL D. WHITE, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital; Boston, Mass.****3:10 Lower Nephron Nephrosis.****WILLIAM GOLDRING, F.A.C.P., Associate Professor of Medicine, New York University College of Medicine; Visiting Physician, Bellevue Hospital; New York, N. Y.****3:30 INTERMISSION.****3:50 Clinical Significance of Cryoglobulinemia.****DAVID P. BARR, F.A.C.P., Professor of Medicine, Cornell University Medical College; Physician-in-Chief, New York Hospital; New York, N. Y.****4:10 Clinical Angiocardiography.****ISRAEL STEINBERG, F.A.C.P., Instructor in Radiology and Medicine, Cornell University Medical College; Assistant Radiologist, New York Hospital; New York, N. Y.****CHARLES T. DOTTER (by invitation), Instructor in Medicine, Cornell University Medical College; Resident in Radiology, New York Hospital; New York, N. Y.****4:30 Diagnosis and Treatment of Pheochromocytoma.****GEORGE F. CAHILL, F.A.C.S. (by invitation), Professor of Urology, Columbia University College of Physicians and Surgeons; Director, Squier Urological Service, Presbyterian Hospital; New York, N. Y.****4:50 ADJOURNMENT.**

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**THIRD GENERAL SESSION****Grand Ballroom, Waldorf-Astoria Hotel****Wednesday Afternoon, March 30, 1949****Presiding Officer****LeRoy H. Sloan, F.A.C.P., Chicago, Ill.****P.M.****2:00 The John Phillips Memorial Lecture: The Natural Occurrence of Anti-thyroid Compounds as a Cause of Simple Goiter.****EDWIN B. ASTWOOD, F.A.C.P., Research Professor of Medicine, Tufts College Medical School; Endocrinologist, Joseph H. Pratt Diagnostic Hospital; Physician, The Boston Dispensary; Boston, Mass.**

**2:45 Therapeutic Possibilities of Para-Aminobenzoic Acid.**

C. J. D. ZARAFONETIS (by invitation), Assistant Professor and Research Associate in the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

**3:05 INTERMISSION.****3:25 Electron Microscopy in Relation to the Medical Sciences.**

STUART MUDD (by invitation), Professor of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia, Pa.

**3:45 Present Status of Aureomycin Therapy.**

MAXWELL FINLAND, F.A.C.P., Associate Professor of Medicine, Harvard Medical School; Associate Physician, Thorndike Memorial Laboratory, and Chief, Fourth Medical Service, Boston City Hospital; Boston, Mass.

**4:05 Chloromycetin and Aureomycin: Therapeutic Results.**

THEODORE E. WOODWARD (by invitation), Associate Professor of Medicine, University of Maryland School of Medicine, Baltimore, Md.

**4:25 Poliomyelitis: Early Diagnosis and Early Management of Acute Cases.**

JOHN R. PAUL, F.A.C.P., Professor of Preventive Medicine, Yale University School of Medicine, New Haven, Conn.

**4:45 The Clinical Features and Laboratory Diagnosis of Rickettsial Pox.**

HARRY M. ROSE (by invitation), Associate Professor of Medicine, Columbia University College of Physicians and Surgeons; Assistant Visiting Physician, Presbyterian Hospital; New York, N. Y.

**5:05 ADJOURNMENT.**


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**FOURTH GENERAL SESSION**

Grand Ballroom, Waldorf-Astoria Hotel

Thursday Afternoon, March 31, 1949

P.M.

**2:00 THE ANNUAL BUSINESS MEETING.**

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary-General, Executive Secretary and the Treasurer; elections of new Officers, Regents and Governors will take place; certain amendments to the Constitution and By-Laws will be presented; President-Elect Reginald Fitz of Boston, Mass., will be inducted as President and will make a brief inaugural address.

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Presiding Officer

Charles F. Moffatt, F.A.C.P., Montreal, Can.

**2:40 Emotional Factors in Organic Disease.**

WILLIAM C. MENNINGER, F.A.C.P., Professor of Clinical Psychiatry, University of Kansas School of Medicine; General Secretary, The Menninger Foundation; Topeka, Kans.

**3:00 INTERMISSION.**

**3:20 The Use of Isotopes as Metabolic Tracers.**

DEWITT STETTEN, JR. (by invitation), Member and Chief of Division of Nutrition and Physiology, The Public Health Research Institute of The City of New York, Inc., New York, N. Y.

**3:40 Therapeutic Considerations in Ulcerative Colitis.**

WALTER L. PALMER, F.A.C.P., Professor of Medicine, University of Chicago School of Medicine, Chicago, Ill.

**4:10 Surgery of the Malignant Tumors of the Ampullary Area and Pancreas.**

ALLEN O. WHIPPLE, F.A.C.S., Clinical Director of Surgery, Memorial Hospital, New York, N. Y.

**4:20 The Treatment of Bleeding Esophageal Varices by Portacaval Shunts.**

ROBERT R. LINTON, F.A.C.S., Assistant Clinical Professor of Surgery, Harvard Medical School; Chief of the Peripheral Vascular Service and Senior Visiting Surgeon, Massachusetts General Hospital; Boston, Mass.

**4:40 The Use of Mixtures of Protamine Zinc and Regular Insulin.**

RANDALL G. SPRAGUE, F.A.C.P., Assistant Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant, Division of Medicine, Mayo Clinic; Rochester, Minn.

**5:00 ADJOURNMENT.**

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**FIFTH GENERAL SESSION**

Grand Ballroom, Waldorf-Astoria Hotel

Friday Afternoon, April 1, 1949

Presiding Officer

A. B. Brower, F.A.C.P., Dayton, Ohio

**P.M.****2:00 The Acute Radiation Syndrome in Man.**

SHIELDS WARREN (by invitation), Director, Division of Biology and Medicine, Atomic Energy Commission; Professor of Pathology, Harvard Medical School; Boston, Mass.

JOHN Z. BOWERS (Associate), Deputy Director, Division of Biology and Medicine, Atomic Energy Commission, Washington, D. C.

**2:30 Gouty Arthritis.**

JOHN H. TALBOTT, F.A.C.P., Professor of Medicine, The University of Buffalo School of Medicine; Director of Medical Service, Buffalo General Hospital; Buffalo, N. Y.

**2:50 Migraine and Histaminic Cephalalgia.**

BAYARD T. HORTON, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in Medicine and Head of Section on Clinical Investigation, Mayo Clinic; Rochester, Minn.

**3:20 INTERMISSION.****3:40 The Etiology of Rheumatic Fever.**

HOMER F. SWIFT (by invitation), Member Emeritus of The Rockefeller Institute for Medical Research, New York, N. Y.

**4:00 Hypersplenism.**

CHARLES A. DOAN, F.A.C.P., Dean, Professor of Medicine and Director of Medical Research, The Ohio State University College of Medicine, Columbus, Ohio.

**4:20 The Treatment of Pernicious Anemia with Vitamin B<sub>12</sub>.**

RANDOLPH WEST, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons; Attending Physician, Presbyterian Hospital; New York, N. Y.

**4:40 ADJOURNMENT.**

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**MORNING LECTURES**

The Morning Lectures recognize the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures enable the speaker to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

Morning Lectures will be offered on Wednesday and Friday mornings only; Hospital Clinics on Tuesday and Thursday mornings only. Two series of Morning Lectures will be presented concurrently in the Ballroom and Starlight Roof of the Waldorf-Astoria Hotel.

The Lectures will be open to all members and guests of the College.

Admission by regular registration badge; no special tickets.

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**Wednesday, March 30, 1949**

**Grand Ballroom, Waldorf-Astoria Hotel**

**Presiding Officer**

**William S. Middleton, F.A.C.P., Madison, Wis.**

**A.M.**

**9:30-10:20 Clinical Implications of Recent Studies of Renal Function.**

HOMER W. SMITH, Sc.D. (by invitation), Professor of Physiology, New York University College of Medicine, New York, N. Y.

**10:20-10:40 INTERMISSION.****10:40-11:30 Treatment of Heart and Kidney Disease and of Hypertensive Vascular Disease with the Rice Diet.**

WALTER KEMPNER (Associate), Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C.

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**Starlight Roof, Waldorf-Astoria Hotel**

**Presiding Officer**

**Maurice C. Pincoffs, M.A.C.P., Baltimore, Md.**

**A.M.**

**9:30-10:20 A Survey of the Actualities and Potentialities of Exfoliative Cytology in Cancer Diagnosis.**

GEORGE N. PAPANICOLAOU (by invitation), Professor of Clinical Anatomy, Cornell University Medical College, New York, N. Y.

**10:20-10:40 INTERMISSION.**

**10:40-11:30 The Collagen Diseases.**

GEORGE BAEHR, F.A.C.P., Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons; Director of Clinical Research and Chief of First Medical Service, Mount Sinai Hospital; New York, N. Y.

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Friday, April 1, 1949

Grand Ballroom, Waldorf-Astoria Hotel

Presiding Officer  
Charles E. Watts, F.A.C.P., Seattle, Wash.

**A.M.**

**9:30-10:20 Viral Hepatitis: Problems and Progress.**

JOHN R. NEEFE (by invitation), Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

**10:20-10:40 INTERMISSION.****10:40-11:30 The Use of BAL in the Treatment of Some Forms of Metallic Poisoning.**

WARFIELD T. LONGCOPE, F.A.C.P., Professor Emeritus of Medicine, Johns Hopkins University School of Medicine; Lee, Mass.

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Starlight Roof, Waldorf-Astoria Hotel

Presiding Officer  
George F. Strong, F.A.C.P., Vancouver, Can.

**9:30-10:20 The Allergy Factor in Disease.**

ROBERT A. COOKE, F.A.C.P., Director of Department of Allergy, Roosevelt Hospital, New York, N. Y.

**10:20-10:40 INTERMISSION.****10:40-11:30 The Response of the Adrenal Cortex to Disease and Injury.**

J. S. L. BROWNE (by invitation), Professor of Medicine, McGill University Faculty of Medicine; Director, University Clinic, Royal Victoria Hospital; Montreal, Can.

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**PANEL DISCUSSIONS**

Topics of intimate interest and practical value to all members of the profession have been chosen. Especially qualified men have been selected as leaders and members of the panel personnel. All panels will be held at the Waldorf-Astoria and are scheduled from Tuesday through Friday, 12:00 M. to 1:15 P.M.

Applications for tickets to panels scheduled in the smaller rooms may be made in advance by members on a regular application form which will accompany the formal program. Tickets will also be available at the Registration Bureau, Silver Corridor, Waldorf-Astoria. Special tickets will not be required for admission to panel discussions in the Grand Ballroom and the Starlight Roof.

Applicants may submit in writing three weeks before the Session, through the Executive Secretary of the College, any questions concerning any phase of the subjects listed. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

## PANEL DISCUSSIONS

	Grand Ballroom (Admission by badge; no tickets.)	Starlight Roof (Admission by badge; no tickets.)	Wedgwood Room Office Floor (Admission by ticket only.)	Le Perroquet Suite Fourth Floor (Admission by ticket only.)	Jansen Suite Fourth Floor (Admission by ticket only.)
Capacity	1,000 I	800 II	500 III	250 IV	150 V
Tuesday March 29 12:00 M. to 1:15 P.M.	Electrocardiography Moderator *Paul D. White Boston  Emanuel Goldberger New York *Gordon B. Myers Detroit Conger Williams Boston *Charles C. Wolferth Philadelphia	Peptic Ulcer Moderator *Henry L. Bockus Philadelphia  *Chester M. Jones Boston *Sara M. Jordan Boston *Walter L. Palmer Chicago Stewart G. Wolf, Jr. New York	Rheumatoid Arthritis Moderator *Russell L. Cecil New York  *Walter Bauer Boston *Edward W. Boland Los Angeles *W. Paul Holbrook Tucson Charles A. Ragan New York	Protein Hydrolysates in Nutrition Moderator *William S. McCann Rochester, N. Y.  Frank W. CoTui New York Sidney C. Madden Atlanta John P. Peters New Haven Sidney C. Werner New York *John B. Youmans Chicago	Management of Thyroid Diseases Moderator *David P. Barr New York  *Edwin B. Astwood Boston *James H. Means Boston Rulon W. Rawson New York Ephraim Shorr New York
	Grand Ballroom (Admission by badge; no tickets.)	Wedgwood Room Office Floor (Admission by ticket only.)	Le Perroquet Suite Fourth Floor (Admission by ticket only.)	Jansen Suite Fourth Floor (Admission by ticket only.)	
Capacity	1,000 VI	500 VII	250 VIII	150 IX	
Wednesday March 30 12:00 M. to 1:15 P.M.	Congestive Failure Moderator *Eugene B. Ferris, Jr. Cincinnati  Harry Gold New York *Dickinson W. Richards, Jr. New York *William D. Stroud Philadelphia *J. Edwin Wood, Jr. Charlottesville	Antibiotics Moderator *W. Barry Wood, Jr. St. Louis  Harry Eagle Bethesda *Maxwell Finland Boston *Chester S. Keefer Boston Colin M. MacLeod New York *Walsh McDermott New York	Management of Poliomyelitis Moderator Thomas M. Rivers New York  John A. Anderson Salt Lake City David Bodian Baltimore James L. Wilson Ann Arbor Jessie Wright Pittsburgh	Medical Diseases of Bone Moderator *Alexander B. Gutman New York  Edward L. Compere Chicago William Parson New Orleans *Edward C. Reifenstein, Jr. New York Isidore Snapper New York	

## PANEL DISCUSSIONS—Continued

Capacity	Grand Ballroom (Admission by badge; no tickets.)	Starlight Roof (Admission by badge; no tickets.)	Wedgwood Room Office Floor (Admission by ticket only.)	Le Perroquet Suite Fourth Floor (Admission by ticket only.)	Jansen Suite Fourth Floor (Admission by ticket only.)
Thursday March 31 12:00 M. to 1:15 P.M.	1,000 X Hypertension Moderator Louis Leiter New York Carl A. L. Binger New York Stanley E. Bradley New York Arthur M. Fishberg New York *Henry A. Schroeder, Sr. St. Louis *LeRoy H. Sloan Chicago	800 XI Diseases of the Liver Moderator *Richard B. Capps Chicago *Edgar S. Gordon Madison *Thomas N. Horan Detroit John R. Neefe Philadelphia Arthur J. Patek, Jr. New York	500 XII Renal Diseases Moderator *George W. Thorn Boston *Maxwell Finland Boston John P. Merrill Boston Edwin L. Prien Boston Donald D. Van Slyke New York	250 XIII Management of Intractable Pain Moderator *Roger I. Lee Boston Ernest M. Daland Boston Harris Isbell Lexington, Ky. Bronson S. Ray New York Harry B. van Dyke New York	150 XIV Hematology Moderator *Cyrus C. Sturgis Ann Arbor Louis K. Diamond Boston *Charles A. Doan Columbus *Russell L. Haden Cleveland Paul Reznikoff New York
Friday April 1 12:00 M. to 1:15 P.M.	XV Anticoagulants for Thrombo-embolism Moderator *Nelson W. Barker Rochester, Minn. *Johnson McGuire Cincinnati *Hugh Montgomery Philadelphia *E. Sterling Nichol Miami *Irving S. Wright New York	XVI Newer Aspects of Allergic Phenomena Moderator *Robert A. Cooke New York Merrill W. Chase New York Alfred Gilman New York Michael Heidelberger New York Paul Klemperer New York	XVII Diabetes Moderator *Randall G. Sprague Rochester, Minn. *Arthur R. Colwell Evanston *Jerome W. Conn Ann Arbor *Alexander Marble Boston *Franklin B. Peck Indianapolis	XVIII Management of Tuberculosis Moderator *J. Burns Amberson New York Frank B. Berry New York *H. Corwin Hinshaw, Sr. Rochester, Minn. Kirby S. Howlett, Jr. Shelton, Conn. *James J. Waring Denver	XIX Use and Abuse of Estrogens and Androgens Moderator Ephraim Shorr New York Earl T. Engle New York *E. Perry McCullagh Cleveland Ira T. Nathanson Boston *Elmer L. Sevringhaus Nutley, N. J.

## THE CLINIC SESSIONS

Clinics and clinical pathological conferences will be conducted on **Tuesday and Thursday only** from 9:15 A.M. to 11:30 A.M., and Morning Lectures will be conducted on Wednesday and Friday mornings, thus eliminating competition between these features of the program. Participating hospitals are listed in the following table, with the days on which they present clinics or clinical pathological conferences. While most of these sessions will be held at the respective hospitals as usual, a number will be offered at the Waldorf-Astoria Hotel. These have been singled out in the table by asterisks.

Adequate accommodations will be provided for all, but admission to most of these sessions will require special tickets which will be issued to members in advance of the Session and to non-members directly at the Registration Bureau in the Waldorf-Astoria Hotel. Application forms for tickets for the clinics and clinical pathological conferences will accompany the formal program to all members.

Emphasis will be placed on clinics in the true sense of that term—that is, patients will be shown and discussed rather than having presentation of formal short papers.

### SUMMARY OF CLINICAL PROGRAMS

Tuesday and Thursday Mornings

March 29 and 31, 1949

HOSPITALS	TUESDAY	THURSDAY
A-1 Bellevue Hospital, Second (Cornell) Medical Division	Clinic	
A-2 Bellevue Hospital, Third (New York University) Medical Division	Clinic	Clinic
A-3 Bellevue Hospital, First (Columbia) Medical Division		Clinic
B Brooklyn Hospital		*Clinic, 10:30-11:30 (Joint session with F)
C Flower and Fifth Avenue Hospitals		Clinic
D-1 Goldwater Memorial Hospital, First Division (Columbia University)	*Clinic, 10:30-11:30 (Joint session with N-1)	
D-2 Goldwater Memorial Hospital, Third Division (New York University)		*Clinic
E Hospital of the Rockefeller Institute for Medical Research	Clinic	
F Jewish Hospital, Brooklyn		*Clinic, 9:30-10:30 (Joint session with B)
G Kings County Hospital	*Clinic	
H Lenox Hill Hospital		Clinic

\* This program to be at the Waldorf-Astoria Hotel. All other clinics will be held at the hospital indicated.



SUMMARY OF CLINICAL PROGRAMS—*Continued*

HOSPITALS	TUESDAY	THURSDAY
J Long Island College Hospital		*Clinic, 10:30–11:30 (Joint session with P-2)
K Memorial Hospital		Clinic
L Montefiore Hospital for Chronic Diseases	*Clinic	
M Mount Sinai Hospital	Clinic	Clinic
N-1 New York Hospital	*Clinical Pathological Conference, 9:30–10:30 (Joint session with D-1)	Clinic
N-2 New York Hospital	Clinic	
O New York University-Bellevue Medical Center, Post-Graduate Medical School and University Hospital	Clinic	
P-1 Presbyterian Hospital	Clinic	Clinic
P-2 Presbyterian Hospital		*Clinical Pathological Conference, 9:30–10:30 (Joint session with J)
R Roosevelt Hospital	Clinic	
S St. Luke's Hospital	Clinic	
T Veterans Administration Hospital, Bronx	*Clinic	

\* This program to be at the Waldorf-Astoria Hotel. All other clinics will be held at the hospital indicated.

A very wide range of medical topics important to the clinician will be offered. In addition to the various aspects of internal medicine, there will be numerous offerings in allied fields. Opportunities will be afforded for visitors to see patients at close range and to observe hospital methods in New York.

The detailed program of clinics is not published in the *ANNALS OF INTERNAL MEDICINE* due to its considerable length, but every detail will be published in the formal program and distributed to all members and to non-members on the official mailing list at the Executive Offices of the College approximately six weeks in advance of the session.

Non-members who wish to be placed on the official mailing list are asked to address The Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

# ABRIDGED MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 7, 1948

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters in Philadelphia, Pa., November 7, 1948, with President Walter W. Palmer presiding, Mr. E. R. Loveland, Secretary, and the following in attendance:

Walter W. Palmer, *President*; Reginald Fitz, *President-Elect*; William S. Middleton, *First Vice President*; Maurice C. Pincoffs, *Second Vice President*; Charles E. Watts, *Third Vice President*; William D. Stroud, *Treasurer*; George Morris Piersol, *Secretary-General*; Ernest E. Irons, William S. McCann, T. Grier Miller, Charles F. Moffatt, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Marion A. Blankenhorn, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, George F. Strong, Walter L. Palmer, *Chairman, Board of Governors*; Franklin M. Hanger, *General Chairman, 30th Annual Session*.

The Secretary read abstracted Minutes of the three meetings of the Board of Regents held at San Francisco, Calif., during the 29th Annual Session, April 19-23, 1948, the Minutes being approved as read.

The Secretary then presented the following communications:

- (1) From absent Regents—Doctors Charles F. Tenney and David P. Barr;
- (2) From Dr. Myron Prinzmetal, Los Angeles, Calif., a former Research Fellow of the College, donating to the College his travel expenses as a guest speaker at the San Francisco Session;
- (3) From Mrs. Ernest B. Bradley, widow of our late President, Dr. Ernest B. Bradley, expressing her deep appreciation for the tribute the College had paid to Dr. Bradley through the sending of flowers and a memorial;
- (4) From the "Seventh Pacific Science Congress," New Zealand, embodying an invitation to the American College of Physicians to send a representative to its Congress in New Zealand during February, 1949;
- (5) From the Assistant Secretary of the Department of State, thanking the College for its coöperation in the preparations for the Fourth International Congresses on Tropical Medicine and Malaria, appreciation being extended also to our official representative, Dr. Joseph M. Hayman, Jr., Cleveland, Ohio, who served on the Organizing Committee;
- (6) From the American Board of Internal Medicine, informing the College that the terms of two of its representatives on that Board, Dr. Roy W. Scott and Dr. Walter L. Palmer, will expire on July 1, 1949; that both are eligible for re-election for a second term of three years on nomination by the Board of Regents.

On motion by Dr. Reginald Fitz, regularly seconded and carried, Doctors Roy W. Scott and Walter L. Palmer were reappointed by the Board of Regents for additional terms of three years, to July 1, 1952;

- (7) From Dr. Ward Darley, College Governor for Colorado, concerning the deductibility of expenses for attending Postgraduate Courses of the American College of Physicians in connection with Federal Income Tax Returns.

The law is so written that expenses for Postgraduate Courses are not deductible on Income Tax Returns, whereas expenses for attending medical con-

ventions are deductible. It was pointed out that the purposes of the Courses of the American College of Physicians are primarily the same as those of its Annual Sessions, namely, the keeping abreast of medical advances in our field. The matter had been placed before the Honorable Eugene Milliken, Chairman of the Senate Finance Committee, who had promised thorough investigation and a later report. It was pointed out that there was essentially no basic difference between a member going to the Annual Session of the College, which we call a "Postgraduate Week," or a member going to one of our one-week courses. The Secretary stated that he had consulted the Treasury Department, inquiring if the name of the Postgraduate Courses might be changed, so that they would be classified the same as conventions, but was informed that this would not be possible. In the discussion that ensued, some pointed out that their Collectors of Internal Revenue had readily allowed deductions for expenses to College Courses, the same as to the Annual Sessions, whereas in other instances the Collector had disallowed such expenses. The matter was left for further information from Senator Milliken;

- (8) From the American Council on Rheumatic Fever. The College representatives on this Council were Doctors Hugh Morgan and William D. Stroud. At the last meeting of the Board of Regents Dr. Stroud had reported that the original purpose of the College representation had probably been fulfilled and there was no further reason for continuing representation by the College, and, therefore, the College had withdrawn. The current communication was from Dr. H. M. Marvin, Chairman of the American Council on Rheumatic Fever, who had enclosed a copy of the Minutes of the last meeting of the Executive Committee of the Council and had stated that the work of the Council had been submerged, due to the reorganization of the American Heart Association. He stated that now that the latter had been completed, the Council was planning to proceed at a more rapid pace and requested the American College of Physicians to reappoint delegates to the Council.

On motion by Dr. Hugh J. Morgan, seconded and regularly carried, Dr. William D. Stroud was reappointed the representative of the American College of Physicians on the American Council on Rheumatic Fever.

The President called for the report of the Secretary-General, Dr. George Morris Piersol. Dr. Piersol reported the deaths since the last meeting of this Board of 1 Master; 40 Fellows; 6 Associates, and the names and dates of death were spread upon the Minutes.

Dr. Piersol then reported that since the last meeting of the Board twelve new Life Members had been added, making a grand total of 720, of whom 58 are deceased, leaving a balance of 662, the names as follows:

Aaron Alfred Sprong.....	Excelsior Springs, Mo.
Walter Howard Wilson.....	Raleigh, N. C.
Olin S. Allen.....	Wilmington, Del.
Harold H. Golz.....	Aramco, Dhahran, Saudi Arabia
Paul Miller Rike.....	Pittsburgh, Pa.
Theodore S. Heineken.....	Bloomfield, N. J.
Edward A. Brethauer, Jr.....	Pittsburgh, Pa.
Philip Reichert.....	New York, N. Y.
Jacob L. Tuechter.....	Cincinnati, Ohio
Gilbert E. Brereton.....	Dallas, Tex.
Jacob Charles Zillhardt.....	Binghamton, N. Y.
John W. Wilce.....	Columbus, Ohio

President Palmer then called for the report of the Executive Secretary, Mr. E. R. Loveland, whose report was as follows:

*"I. New Building Addition:*

This has been completed in a thoroughly satisfactory manner, and it makes available wholly adequate space for the College Staff, with provision for expansion for a long time. The more noisy activity, such as addressographing, duplicating and mailing, has been placed in the basement room. The general stenographic staff is on the first floor, and the second floor provides a fine meeting room, which is being considered for such use as Postgraduate Courses, Regional Meetings, etc. The room, however, has not yet been furnished with chairs, lectern, etc., because the House Committee wishes to consult with the Board of Regents. You will hear about this from the House Committee later.

*"II. Regional Meetings:*

Twenty-three Regional Meetings have been held, or are definitely scheduled, during the current year. The list of the meetings has been duplicated for your information. In general, these Regional Meetings have improved from every point of view; with better programs, larger attendance, more enthusiasm. Dr. Palmer, as President, and various members of the Board of Regents have been highly coöperative in representing the administrative office of the College at these various meetings. We are thoroughly convinced that they make a real contribution to the more active participation of members. The Regional Meetings give many of the younger members opportunities to appear on the programs, whereas they might never have that opportunity at the Annual Sessions. Furthermore, members become better acquainted with one another, and certainly obtain a better understanding of the objectives of the College and the standards of admission. The cost of the Regional Meetings, considering the number thereof, is essentially nominal. For instance, it is estimated that the total cost at the end of this year will be a little over \$1,700.00.

*"III. The San Francisco Annual Session:*

I need not refer to the very successful program and to the arrangements at the San Francisco Session, because all of the Regents were there. We had a gross registration of 3,374, which was the third largest registration in the College history, being exceeded only by the Philadelphia (1946) and Chicago (1947) meetings, where the gross registration was 4,037 and 4,410, respectively. It is interesting to note in analyzing the registration, however, that more than half of the registration at the Annual Meetings is made up of guest physicians, senior medical students, exhibitors and ladies. To be sure, many of the guest physicians are guests of members of the College, but there would be no great problem in handling the Annual Meetings of the College if the attendance were limited to members. That remark is made as an observation and not as an intimation that such restriction should be initiated. The cost of the San Francisco Session was greatly in excess of that of any other previous meeting, the gross cost being \$34,147.00, compared with Chicago (1947), \$23,488.00, and with Philadelphia (1946), \$14,865.00. We received the largest gross income from Exhibits at San Francisco of any meeting we have had, but with the expenses deducted, the net income was only \$16,774.00. The income from Guest Fees was \$1,249.00, and we had a net deficit of over \$16,000.00, compared with the net deficit in 1947 of slightly over \$5,000.00 and with a net surplus in

1946 of slightly over \$5,000.00. The largest increments in expenses at San Francisco were for rental of the auditorium and for the travel expenses of the Regents, Officers and non-member Speakers. You will receive a detailed, comparative cost analysis with the financial statements later on in this meeting.

*"IV. Annals of Internal Medicine:*

The circulation of the 'ANNALS' continues to grow. We are at present printing 12,200 copies per month, with the prospect of having to increase the order in the near future. A year ago the circulation was 11,078. This is more than 100% increase in circulation since 1940. You will find, however, when you receive the report from the Committee on the Annals of Internal Medicine that our printing costs since 1940 have actually increased basically about 100%, and that we face an immediate further increase of approximately 24%. Add to this the consideration that we have been increasing the volume or number of pages of the 'ANNALS' materially, and you will appreciate that our net income is now starting to descend sharply. A year ago, with a thousand less circulation, we had a surplus of over \$32,000.00; for the current year, ending June 30, the surplus had decreased to \$25,000.00. A year ago the basic printing costs were slightly less than \$34,000.00, and for the past year it has increased to over \$45,000.00—partly due to the increased basic costs by the printer and partly due to the increased number of copies and the increased size of the journal.

Another observation I would make is that our advertising income is starting downward, although only \$1,500.00, during the past year. In the immediate post-war period firms were avaricious in their advertising policies. Now they report that their incomes are decreasing, their expenses increasing, and, therefore, their advertising program being curtailed. We shall have to extend greater effort in attempting to hold up the advertising income.

I do not wish to transgress on the report that will come later from the Committee on the Annals of Internal Medicine, but I would like to observe at this point that all other publishers of medical journals have long since been adjusting their subscription price to the cost of publication. Some medical journals have advanced their subscription prices as much as \$5.00 per annum, and most of them have had at least one or more advances in the subscription price during the past two years. The subscription rate for the 'ANNALS' stands today at the same rate it was twenty-two years ago when the journal was much smaller and when the costs were less than one-half of the present rates. I might mention, however, that we have advanced our advertising rates once since the War.

*"V. Candidates for Membership:*

The number of candidates for Associateship now has attained about the same level as that at the outset of the War and the prospects are that there will be an ever increasing number of proposals as time goes along. The number of candidates for advancement to Fellowship is more limited at present than at the outset of the War, because smaller groups of Associates were elected during the war years, and, therefore, there is a smaller number eligible at present to come up for Fellowship. By 1951, however, the number coming up for Fellowship will have resumed its former level and will regularly rise thereafter, unless more restrictive requirements are initiated.

*"VI. Postgraduate Courses:*

This activity for the current year has been on a more or less comparable basis with 1947. The courses still remain extremely popular, and the appreciation of the members appears to grow. We were gratified in receiving a letter from a professor in one of our important medical schools recently, in which he expressed the opinion that the College has attained a topmost position in this type of postgraduate education in the country. Perhaps we have been too prone to fail to attach adequate importance to this activity of the College, because the courses are short and scattered. The report of the Committee will reveal many interesting features of this program.

*"VII. Membership Roster:*

During the past summer we published, in accordance with directions of the Regents, a new and revised Membership Roster. It cost, however, nearly \$4,000.00, which includes postage of some \$600.00. There continues to be a desire and need for a complete College Directory, but the publication of such a Directory under present conditions would involve a cost at least of \$17,000.00, a figure which causes us to consider seriously the propriety of publishing a Directory during 1949. That is a matter that must be determined by the Board of Regents and probably should not be discussed at this point, but in connection with the report of the Committee on Finance and the adoption of budgets for 1949."

Mr. Loveland then introduced a discussion of the advertising policies, and stated the "ANNALS" was sometimes criticized by advertisers because of its highly restrictive policy in refusing the acceptance of advertising of any pharmaceutical product which has not yet been accepted by the Council on Pharmacy and Chemistry.

Dr. Piersol, Chairman of the Committee on Advertising, said he had discussed the matter at length with Mr. Pindar, who is handling the advertising for the "ANNALS," and pointed out that there are some of the large, reputable drug houses who, for instance, manufacture penicillin, but who can no longer make a profit from advertising this product as "penicillin," because the name does not in any manner distinguish their product from that of their competitors. Yet, the regulations of the Council may prevent the manufacturer from using a special trade name for his brand. If such were done, his brand of penicillin would not be acceptable for advertising in the "ANNALS," or any of the other journals which support the Council on Pharmacy and Chemistry. Dr. Piersol expressed the belief that there is some question whether the average physician actually pays any attention to whether some of the better preparations are either approved or disapproved by the Council. He suggested that this complicated subject should be carefully considered, and possibly some modification made, and that a committee be appointed to explore the whole subject before the next meeting of the Regents, and that they be requested to bring in a report with more factual data on which the Regents might take some action to modify the present rule.

On motion by Dr. George Morris Piersol, regularly seconded and unanimously carried, his recommendation was approved.

The Board at this point took up a discussion of that part of the Secretary's report concerning the publication of a Membership Roster or of a completely revised Directory during 1949. It was pointed out that there is a persistent request among members for the republication of a full Directory of the College. The College has been a rather generous organization. Although its dues are comparatively small, it has given in the past without charge to its members the journal, the Membership Roster or Directory and many and all other publications. Numerous other societies retain the dues exclusively for the maintenance of its organization and annual meetings and

charge their members for their publications. Although operating costs have increased nearly 100 per cent, the dues, though increased  $33\frac{1}{4}$  per cent over the "depression" period, are still at the same level as in 1929. The thought was advanced by the Secretary that while the Membership Roster might continue to be given to members without charge, the Directory, to cost between \$17,000.00 and \$20,000.00, might be sold to members at pro rata cost price on a pre-publication order plan, or at approximately \$4.00 per copy, postpaid. He pointed out that such a price was small and most reasonable in comparison with charges made for ordinary directories. The matter was left for further consideration at the time of the receipt of the report of the Committee on Finance.

President Palmer then called for the report of the Committee on Credentials, Dr. George Morris Piersol, Chairman.

Dr. Piersol reported that the Committee on November 5-6, 1948, had reviewed the credentials of 204 candidates for Associateship and 131 candidates for Fellowship. Of this number, the Committee recommended the election to Fellowship of 81 candidates, and of the election to Associateship of 215 candidates, 11 of whom had actually been proposed for direct Fellowship.

The recommendations for election were approved by formal resolution, and the names of 81 new Fellows and 215 new Associates were spread upon the Minutes.

Dr. Piersol further presented the names of Associates, elected during the war years, who were entitled to extension of time to qualify for Fellowship, and recorded the names of Associates who had to be discontinued on the Roster, because of failure to qualify for Fellowship.

A summary report on the candidates elected to Associateship on November 20, 1943, was as follows:

Already Advanced to Fellowship .....	87
Resigned .....	1
Dropped for Failure to Qualify .....	13
Term Extended due to Military Service .....	37

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Total, Candidates elected November 20, 1943 ..... 138

Continuing his report, Dr. Piersol stated that the Committee on Credentials and the Executive Committee of the Board of Regents would convene a day earlier at the New York Annual Session in March, 1949, for the purpose of reviewing two proposals under consideration—(1) that the College be restricted to Internists; (2) that certification be a prerequisite for Associateship—with the hope that out of such a meeting would come solid recommendations upon which the Board of Regents may act.

The Committee on Credentials had received a communication from an Associate, elected May 12, 1946, who due to graduation from a medical school in Germany had been refused admittance to the examinations of the American Board of Internal Medicine, and who, therefore, will be unable presumably to qualify for advancement to Fellowship. The Committee stated that it knew of no remedy that the College could offer to assist this candidate.

The Committee also received a communication from a physician in Manila, who requests that something be done to make physicians from the Philippine Islands eligible for membership in the College. Dr. Piersol pointed out that it has been a long established policy to restrict membership to citizens of North America, and since the Philippine Islands are wholly outside of our territory now, we can only inform the gentleman that physicians from that Country are not eligible in our College at the present time.

On recommendation of the Committee on Credentials, unanimously approved by the Board of Regents, Dr. Christian Bateman Luginbuhl, of Des Moines, Iowa, was reinstated as a Fellow of the College.

The complete report of the Committee on Credentials was accepted as a whole.

Dr. William D. Stroud, Chairman, reported for the House Committee.

The entire building appropriation of \$55,153.87 had been expended, but actually some funds had been used for semi-furnishing items, such as venetian blinds, window shades, screens, plastic flooring, landscaping, etc. He reported also the purchase of some items of equipment, amounting to \$656.35, approved by the Committee.

He said the Second Floor Meeting Room could readily be equipped to accommodate Postgraduate Courses and Regional Meetings of the College, and that the House Committee was prepared to recommend the purchase of chairs, lectern, coat and hat racks, and other necessary equipment. The Committee presented specific recommendations for needed items of plumbing, painting and papering, totalling an estimated expense of \$1,260.00.

The Committee also recommended that the property adjoining the College Headquarters, owned by the College, shall have such repairs and replacements as are minimally required for the time being.

He reported that the Committee had examined the budget for the College Headquarters for 1949, and recommended its adoption.

By formal resolution the report of the House Committee was received, and its recommendations approved.

President Palmer then called for the report of the Committee on Masterships, Dr. William S. Middleton, Chairman.

"The Committee on Masterships met yesterday, reviewed the subject of the qualifications for Masters and was agreeable to the general opinion that these Masters should represent only individuals who have been outstanding in the field of medicine, who have given materially to the College and who have attained not only national but international reputations. The Committee, furthermore, talked over the question of the appearance of the nominees at the Convocation at which the distinction would be awarded, and it was the feeling of this Committee that, unless there are unusual circumstances, making it impossible for the designated individuals to appear, such Masterships should not be granted. This imposes upon the Officers of the College the decision as to what constitutes an extenuating circumstance. It is perfectly apparent that if a Mastership in the College is to attain or to maintain the dignity of an honorary degree, in keeping with the practice of recognized institutions of learning, the honorary degree shall not be granted in absentia.

"The Committee recommends for the distinction of Masterships in 1949:

Dr. George Dock .....	Altadena, Calif.
Dr. Elliott P. Joslin .....	Boston, Mass.
Dr. Jonathan C. Meakins .....	Montreal, Que., Canada
Dr. Virgil P. Sydenstricker .....	Augusta, Ga.
Dr. James J. Waring .....	Denver, Colo."

After general discussion, on motion by Dr. William S. Middleton, seconded and regularly carried, the report and recommendations of the Committee on Masterships were approved.

Dr. Ernest E. Irons, as Chairman, made the following report for the Committee on Public Relations:

"I. *Communications:*

"(a) Gorgas Memorial Institute of Tropical and Preventive Medicine.

The College is interested in this because our President is an ex officio member of the Institute; otherwise we have no special



interest. The report from the Institute is received and the acknowledgment of the report is sufficient; no action recommended;

"(b) World Medical Association, Dr. Louis H. Bauer, F.A.C.P., Secretary-Treasurer.

Dr. Bauer wrote to President Palmer. The World Medical Association was formed originally through the action of English, French, American and Canadian physicians. There are both organizational and individual memberships. Each member will receive a certificate of membership and will receive the publications of the World Medical Association and of the United States Committee. Organization members may also submit problems of international interest or their particular fields for study by the Association. In the early organization of the World Medical Association it was recognized that most of the nations of Europe would be limited in their finances, and that some method might have to be devised to finance any significant program. Thus a United States Committee was formed as an auxiliary financial agent. On the Board of this Committee are five or six doctors and four or five representatives of manufacturing interests. It has required something over \$50,000.00 to finance this organization, including the financing of its headquarters in the New York Academy of Medicine under the Secretary-Generalship of Dr. Louis H. Bauer.

The American Medical Association, the International College of Surgeons, the Mayo Clinic, the American Red Cross and the National Foundation for Infantile Paralysis, and numerous organizations allied to medicine, have become members. The United States Committee would be glad to have the American College of Physicians to become a sustaining member, and it is hoped that those who accept membership will remain members for at least five years. The members enumerated above have each agreed to contribute \$2,000.00 a year; others are contributing from \$1,000.00 to \$10,000.00 a year. The College is being requested to contribute an amount in proportion to its membership and financial status, the exact amount to be determined by the Board of Regents. In so doing, the College may feel that it is helping to improve medical health standards throughout the world, and to improve international medical relations, and to be able to use the facilities of the World Medical Association for investigation of some problems within the field of our College.

The World Medical Association has the blessing of our State Department and is an auxiliary medical effort, which will take up questions that the World Health Organization cannot consider by reason of its political union with the United Nations.

Our Committee recommends to the Regents that the American College of Physicians participate in the World Medical Association and contribute the amount of \$2,000.00 per year for five years."

Dr. Irons moved approval of the recommendation, and it was seconded and opened for discussion, but after extended discussion, the motion was laid on the table for further consideration later in the meeting, at the time of the report of the Committee on Finance.

Dr. Irons continuing his report:

- "(c) Ada P. McCormick, Editor & Publisher of 'Letter'—telegram concerning the Kinsey report.

The Committee recommends merely that the telegram be filed.

- "(d) The Pennsylvania Radiological Society. .

The correspondence includes the resolution of May 22, 1948, of the Pennsylvania Radiological Society, directed to the House of Delegates of the American Medical Association. The Committee wishes to express itself in sympathy with the importance and complexity of this problem. In keeping with the previous policies of the College, however, the Committee feels that action in the problem should be referred to the American Medical Association. The problem referred to is one involving support of radiologists in their controversy with hospitals.

- "(e) Prof. A. Gigon, Basel, Switzerland, regarding the organization of the International Society of Internal Medicine.

The Committee reaffirms the opinion expressed at a previous meeting of the Board of Regents to the effect that inasmuch as the World Medical Association is in process of organization and function, there is no immediate reason for promoting another organization at this time.

- "(f) Riverside County Medical Association, concerning the advertisement in the local newspaper by a Fellow of this College.

The Committee regards the advertisement as a breach of ethics which a Fellow of the College should not engage in, and recommends that a letter be sent, expressing this view, but asking for any explanation he may have in the matter."

On motion by Dr. Irons, seconded and regularly carried, this section of the report was approved.

#### "II. *Fees and Dues Cases:*

Dr. Irons reviewed the cases of 3 Fellows who had retired from practice or other remunerative medical work, due to physical disability, and on recommendation of the Committee, with the approval of the Regents, dues were waived beginning January 1, 1949, and until recovery and resumption of work.

#### "III. *Resignations:*

The Committee has reviewed the resignations of Dr. Morgan J. Foster (Associate), Cedar Rapids, Iowa; Dr. William L. Wheeler (Associate), New York, N. Y.; and Dr. Horace Pettit (Associate), Gladwyne, Pa., and recommends acceptance of all three."

On motion by Dr. Irons and duly carried, this section of the report was approved.

#### "IV. *Establishment of Honorary Fellowships:*

The Committee has considered the establishment of Honorary Fellowships, and recommends to the Regents that a category of Honorary Fellowships be approved in principle by the College. This matter comes up in connection with a request from Dr. Noble Wiley Jones, and others, for the College to provide Honorary Fellowships for distinguished persons from

other countries. The Royal Australasian College of Physicians has honored Dr. Noble Wiley Jones and Dr. Hugh J. Morgan with similar Fellowships. If the Board of Regents approves of this recommendation, the Committee on Constitution and By-Laws will provide the amendments."

There followed long discussion of the matter, and questions were raised as to whether an Honorary Fellowship would be granted in absentia, or whether the candidate would have to be present; whether it might be limited to especially distinguished guests invited to appear on our Annual Session programs; whether it be considered merely a distinction conferred, because of accomplishment, on some foreign physician; and whether the College would be subjected to undue pressure creating difficult situations; whether it should be limited to a very small number of individuals. Dr. Irons was asked to submit the wording of the amendment to the By-Laws in case the proposal was adopted.

Dr. Irons, also Chairman of the Committee on Constitution and By-Laws, presented the following recommendation:

"The Committee on Constitution and By-Laws recommends that Article IV of the Constitution shall be amended by changing the introductory sentence to read 'Members of the American College of Physicians shall be of three classes: (a) Fellows; (b) Masters; and (c) Honorary Fellows,' and by adding a new section, 'Section (c). Honorary Fellows. Honorary Fellows shall be internists, members of the medical profession of countries other than the United States or Canada, who on account of personal character, positions of honor and influence, or eminence in the practice of internal medicine or in research, shall be recommended by the Committee on Masterships to the Board of Regents. Honorary Fellows shall not have the right to vote or to hold office.'"

"The Committee also recommends amending Article IV, Section (b) by reversing the order of the words 'influence and honor' to read 'honor and influence.'"

"The Committee also recommends amending Article VI of the By-Laws: amending the title to read 'Election of Masters and Honorary Fellows'; numbering the first paragraph '(a),' and adding paragraph '(b) The Committee on Masterships may also present to the Board of Regents nominations for the election of Honorary Fellows. Not more than two Honorary Fellows shall be elected in any calendar year.'"

On motion by Dr. Irons, on behalf of the Committee on Public Relations, and duly seconded, a resolution was adopted approving of Honorary Fellowships and authorizing the proper amendments to the Constitution and By-Laws. Then a series of formal resolutions were adopted approving of each amendment to the Constitution and By-Laws. It was further recorded that, as a regulation of the Board of Regents, no dues shall be exacted from Honorary Fellows.

#### *"V. Eligibility for College Membership:*

##### *"(a) Veterans Administration Physicians.*

Heretofore Veterans Administration Physicians were blocked from admission to the American Board of Internal Medicine examinations in those localities where they were not eligible for membership in county and state medical societies and the American Medical Association. So far as the Committee on Public Relations knows at present, Veterans Administration Physicians can now join the American Medical Association by special action of that body, and, therefore, can be admitted to the examinations of the American Board of Internal Medicine.

Unless other evidence develops, the Committee recommends no action.

- “(b) Physicians from North American Countries, other than Canada and the United States.

Heretofore these physicians were blocked from membership in the College, because they are not eligible for admission to the examinations of the American Board of Internal Medicine, due to lack of membership in the American Medical Association or the Canadian Medical Association.

This is a defect possibly in the regulations of the American Board of Internal Medicine and of the American College of Physicians. The Committee suggests that this matter be deferred until further information can be obtained from the American Board of Internal Medicine. The Committee points out that Direct Fellowship in the College is still available to distinguished physicians from such countries.

*“VI. Fees and Dues of Medical Officers in the Army, Navy, Public Health Service and Veterans Administration (referred to the Committee on Public Relations by the Board of Regents at San Francisco, April 20, 1948).*

A number of schedules of salaries available to the various ranks in the Army, Navy, Public Health Service and Veterans Administration, and salaries paid to full-time teachers of medicine has been studied.

The Committee recommends that, under interpretations by the Board of Regents of the By-Laws, pages 14 and 15 of the informative booklet, the two paragraphs under ‘Class D—Special cases falling in one or more of the above classes (Class A, practicing clinicians; Class B, whole-time teachers or research workers with salaries of \$5,000.00 or more; Class C, whole-time teachers and research workers with salaries of less than \$5,000.00)’ shall be deleted, and that Medical Officers in the Army, Navy, Public Health Service and Veterans Administration be considered under Classes B and C.

The Committee also recommends that minimal dues be increased from \$10.00 to \$12.00, thus revising Class B and Class C accordingly.”

On motion by Dr. Irons, duly seconded and carried, this section was approved, and the report was adopted as a whole.

Dr. Reginald Fitz, Chairman, presented the following report for the Committee on Fellowships and Awards:

“Our Committee has remembered the basic purposes of Research Fellowships. The By-Laws state that Research Fellowships are established ‘to promote and advance clinical research’ and are designed especially for the benefit of young physicians who are in the early stages of preparation for a teaching or investigative career in medicine.

“This year we have reviewed the records of thirty-three (33) applicants, and believe that eight (8) deserve Research Fellowships from the College. These candidates are:

*James K. DeVore*; 25; a graduate of Oklahoma in 1947; a veteran; who hopes to work under Dr. Irvine H. Page, at the Cleveland Clinic, on general problems related to hypertension; \$2,200.00.

*Stefan S. Fajans*; 30; a graduate of Michigan in 1942; a veteran; who hopes to work under Dr. Jerome W. Conn, University of Michigan, upon physiological mechanisms capable of stimulating or depressing the Islets of Langerhans; \$3,000.00.

*Horace W. Gerarde*; 29; a graduate of Wisconsin in 1948; who hopes to work under Dr. N. A. Womack, University of Iowa, on the histochemistry of certain liver diseases; \$3,200.00.

*John C. Laidlaw*; 27; a graduate of Toronto, 1944; a veteran; who hopes to work under Dr. F. G. Young, University College, London, England, on metabolism of certain cholinesterase inhibitors in relation to myasthenia gravis; \$2,200.00.

*James Metcalfe, Jr.*; 26; a graduate of Harvard in 1946; a veteran; who hopes to work under Dr. E. M. Landis at Harvard on the dynamics of the circulation under various conditions; \$3,200.00.

*Samuel Moore Peacock, Jr.*; 26; a graduate of Pennsylvania in 1948; who hopes to work under Dr. Robert Hodes at the University of Pennsylvania on the cytochemistry of nervous tissue during growth and other physiological activity; \$2,200.00.

*Jack L. Strominger*; 23; a graduate of Yale in 1948; who hopes to work under Dr. O. H. Lowry at Washington University on the microchemistry of the brain tissue; \$2,200.00.

*Edgar Woody, Jr.*; 29; a graduate of Johns Hopkins in 1944; a veteran; who hopes to work under the Departments of Medicine and Pathology at Vanderbilt University on the combined effect of potassium iodide and streptomycin in experimental tuberculosis; \$2,200.00.

"Of these young men, the Committee has selected Dr. John C. Laidlaw as the Alfred Stengel Research Fellow, since in their judgment he offers greatest promise of attaining unusual distinction in investigation, teaching and as a clinician.

"The stipends recommended for these fellows will vary to meet individual needs. It may be of some interest to note that none of the thirty-three (33) applicants expressed any interest in working on isotope problems.

"The Committee asks that \$17,400.00 be set aside for Fellowships in the 1949 Budget, and for permission to use an unexpended sum of \$3,000.00, freed in 1948 by a Fellowship granted, but not accepted.

"The Committee is gratified to report that six Fellows appointed to begin their Fellowships on July 1, 1948, are happily at work, and that follow up notes on previous Fellows continue to prove the value of Fellowships.

"The Committee has selected to receive the John Phillips Memorial Award for 1949 Dr. Edwin B. Astwood, Professor of Experimental Medicine at Tufts Medical College, Boston. His work in introducing antithyroid drugs represents an outstanding piece of work in Internal Medicine; it has had a direct bearing on the advancement of Clinical Science by opening numerous channels of exploration to other investigators.

"The Committee, after obtaining the advice of the President and Fellows consulted, because of their expert knowledge in the field of Preventive Medicine, nominates to the Board of Regents as second recipient of the James D. Bruce Memorial Award Dr. Stanhope Bayne-Jones, of New York. His many talents and his broad interests in a variety of aspects of public health make him seem a suitable candidate.

"Through Dr. Sturgis the Kellogg Foundation has made an interesting approach to the College. The Committee considers the matter of considerable importance, and has directed the Chairman to ask the Regents to allow Dr. Sturgis the privilege of the floor, so that he may present to the Board the Foundation's proposal."

On motion by Dr. Reginald Fitz, duly seconded and unanimously carried, all recommendations of the Committee on Fellowships and Awards were approved, and the report adopted as a whole.

Dr. Fitz then introduced a discussion of a proposal by the W. K. Kellogg Foundation, to set up American College of Physicians' Latin-American Fellowships, the matter having first been presented to Dr. Fitz by Dr. Cyrus C. Sturgis.

Dr. Sturgis explained that the Kellogg Foundation, of Battle Creek, Mich., has been established for about twenty years, has assets of some sixty-six million dollars, and has as its primary interest the medical betterment of the world. Their activities

began in Michigan and spread over the United States and now through Mexico, Central and South America. Dr. Benjamin G. Horning, Director of the Division of Medicine of the Kellogg Foundation, would like the College to take six young men from Central and South America who are interested in Internal Medicine for one or more years' fellowships in the United States, after which they will be guaranteed teaching positions in their home lands. These men thus selected would have their way paid partially by the State Department, and the Kellogg Foundation would pay their fellowship expenses. Many of them would first be taken to the University of Michigan for language study for a month or two, and then assigned to the formal fellowships for a study period of a year, and the program would start in the autumn of 1949, if approved by the College. The selection of the candidates would be made by Dr. Horning through personal contact with the various medical schools and hospitals in the countries from which the candidates come, and the College would have the right to select six of the group of nominees. Dr. Sturgis pointed out that in the past there has been some criticism because candidates for medical training from South and Central America have been largely unsponsored, unasked and precipitated upon us, creating quite a task. Some have been unable to speak English; some of them have not had adequate scholastic standing; and some institutions, therefore, have not had satisfactory experience with them. Under this plan they would be formally sponsored by the College, the Kellogg Foundation and the State Department; they would be carefully selected; and they would be carefully supervised while in America. It would cost the College nothing financially, but would require time in the selection of the men and in the location of institutions where they will be accepted. Dr. Sturgis recommended the proposal as a means for the American College of Physicians to extend its influence. He pointed out that the Kellogg Foundation is interested in very many things in common with the College, such as postgraduate education.

In the discussion that followed, Dr. Walter L. Palmer suggested that the required period for the study of English be increased to three or four months, and that the term of the fellowship should in many instances be longer than a year. Dr. Palmer had had a considerable experience with fellows from the Latin-American countries and felt that they often had inadequate time for medical training after attaining a working knowledge of English. He considered it utter folly to bring these men to America unless they will have adequate time for necessary training.

Dr. Sturgis expressed the opinion that the appointments by the College be made from year to year, and expressed the feeling that the Kellogg Foundation would be glad to extend fellowships in individually merited cases for two, three or more years.

Dr. Maurice C. Pincoffs pointed out that heretofore the American College of Physicians' regular Research Fellowships were awarded to men who could themselves locate acceptable institutions that would accept them for study, and the College would pay the bill, whereas in this case the policy is reversed, the College is to find them the place to work and the Kellogg Foundation will pay the expenses.

Dr. William S. Middleton said that he had reviewed the Kellogg Foundation's proposal and believed it entirely sound, with certain limitations, such as pointed out by Dr. Pincoffs, and he predicted the program could readily be made effective.

On motion by Dr. Cyrus C. Sturgis, duly seconded, a resolution was adopted, providing that the Board of Regents approve of the proposal in principle; also on a motion by Dr. Sturgis, duly seconded, a resolution was adopted that the matter be referred to the Committee on Educational Policy for recommendations as to procedure.

Dr. Hugh J. Morgan, Chairman, presented a brief report of the work of the American Board of Internal Medicine. He said the basic mission of the Board is being carried out, that the Board is contributing to the elevation of standards and the practice of Internal Medicine in this country. He spoke of the need for some agency to survey the qualitative needs of the country with relation to internists, and such a survey would enable the Board to operate far more intelligently. The Board is

conscious, he said, of its responsibilities. Hospitals throughout the country, in many instances, insist upon certification before staff appointments are made; many medical schools require certification before appointment on the faculty or the staff. The Board also, he stated, had added responsibilities thrust upon it by the College, because certification is one of the College requirements for membership. The technical operation of the Board, with respect to its two types of examinations, is in a satisfactory state; 1,180 candidates had taken the written examination during 1948; about 66 per cent passed and about 34 per cent failed; 730 candidates had taken the oral examination, and about 75 per cent had passed and 25 per cent failed.

Dr. Morgan reported also that the Board had recommended to the Council on Medical Education and Hospitals of the American Medical Association that that Council should appoint consultants throughout the country to inspect hospitals for the determination of their qualifications for resident training programs. The Council has not been able up to the present, he said, to provide an adequate mechanism for hospital inspection. That inefficiency had reflected itself on the operation of the Board, for the Board has been asked to approve or disapprove hospitals for resident training, but the Board has no operating facility for that work. The Conference Committee, consisting of representatives from the College, the Board and the Council, has been reactivated, and both the Board and the College will assist in the nomination of consultants to help the Council in its program.

Dr. Ernest E. Irons inquired whether or not the American Board of Internal Medicine could properly help share the expenses of the hospital program, and Dr. Morgan expressed the opinion that the Board would be willing, within its economic ability.

By resolution Dr. Morgan's report on the American Board of Internal Medicine was accepted.

Dr. William S. Middleton, as Chairman, reported for the Committee on Educational Policy and for the Advisory Committee on Postgraduate Courses. He stated that the attendance at the College courses for the year 1948 had been most gratifying—485 for the spring courses and 478 for the autumn courses. It has been customary, he said, to collect reports from the registrant concerning each course, in an attempt to obtain constructive criticism for the improvement and extension of the postgraduate program. The Committee believed that it would be more effective if in the abstracts of the report the names of the writers be excluded, the feeling being that there may be some hesitancy on the part of an individual to comment unfavorably on the content, presentation of given material, etc. The Committee had observed, however, that all criticism has appeared to be perfectly open and constructive, and certainly helpful. The Committee had reviewed proposed courses for the near future, and announced the schedule for the spring of 1949 (already previously published).

Dr. Middleton then stated that the Committee had recommended that the American College of Physicians go on record as strongly supporting the position of the American Board of Internal Medicine in its position that fundamental certification in Internal Medicine must continue to be a prerequisite for later certification in several of the sub-specialties of Internal Medicine.

The Committee also was of the opinion that the duplicating of subject material at the graduate courses offered by the College cannot be reproduced for the registrant or for circularization. Every member of the Committee present who had experience in this field believed that it would be a deterrent to effective teaching, a deterrent to the organization of courses in the future, to require prior preparation for reproduction of subject material. The Committee had information at hand indicating that some of the directors would withdraw from the program if the College thrust upon them responsibility for the reproduction of the subject material in their courses—a chore so great that it would preclude the possibility of their directing courses. The Committee felt, however, in individual cases the College might grant permission for the

reproduction of the material, such as in the case of the course in Gastro-enterology at Philadelphia during December, 1948, under Dr. Henry L. Bockus, where overtures and assurances from a local publishing house had been received, stating their willingness to underwrite the publication of this course.

Dr. Maurice C. Pincoffs raised a question in connection with the publication of course subject material, saying that he interpreted it as meaning that subject material would not appear as a publication sponsored by the College, but as a publication sponsored by the individual.

On motion by Dr. William S. Middleton, duly seconded, the report of the Committee on Educational Policy and of the Advisory Committee on Postgraduate Courses was adopted.

Dr. T. Grier Miller, Chairman, presented the report for the Committee on the Annals of Internal Medicine, stating that the cost per page for printing the journal had been increased 23 per cent as of November 1, thus making an average of 94 per cent increase since 1940. Although the number of pages per year had increased only by 122, the overall cost, exclusive of the new 23 per cent rise, had increased from \$21,800.00 to \$45,300.00—almost 99 per cent. Because of a greatly increased circulation, however, a surplus had thus far been maintained, although the surplus for Volumes XXVII-XXVIII had decreased some \$7,000.00 from that for the two immediately preceding Volumes, XXV-XXVI. The new increase in printing costs, Dr. Miller predicted, would reduce this surplus an additional \$10,000.00 in 1949—still further, if further costs are imposed or advertising is curtailed. He pointed out that the subscription price of other medical journals has been increased from 16½ per cent to 60 per cent, whereas the ANNALS' subscription rate has never been changed since the journal was founded in 1926. The Committee on the Annals of Internal Medicine therefore recommended that the basic subscription rate be raised from \$7.00 to \$10.00 for domestic circulation and to \$11.00 for foreign circulation, and that in the case of members of the College, \$9.00 of their dues shall be assigned to the ANNALS account.

The Committee on the Annals also recommended that personal news items shall be omitted from the journal, and the News Section largely restricted to Minutes of the Boards and Committees, notices of Regional Meetings and Postgraduate Courses, and other items of national importance to the College.

The Committee also recommended that books selected by the Editor as suitable for Review be submitted to competent Fellows or Masters of the College throughout the country, who shall be requested to prepare critical reviews promptly and without compensation, their names to be published in full in connection with the review.

Finally, the Committee expressed its commendation of Dr. Maurice C. Pincoffs, the Editor, for his efficient management of the editorial affairs of the journal.

The report and recommendations of the Committee on the Annals of Internal Medicine were unanimously approved.

Dr. Maurice C. Pincoffs, as Editor, presented a brief report, stating that the quality of material received for the ANNALS in the last year had greatly exceeded that of previous years.

Dr. LeRoy H. Sloan reported for the Conference Committee on Graduate Training in Medicine, stating that he had met with the Council on Medical Education and Hospitals, and with the American Board of Internal Medicine, and had held conferences with Dr. Donald Anderson, Secretary of the Council. The actual accomplishments of the Committee had been the reactivation of the coöperative plan among the Council, the American Board and the College, with two members of each agency forming a committee. They had been concerned chiefly with the matter of approval of hospitals for residencies in Internal Medicine. The Committee believed that if an approved list bearing the stamp of approval of the College, the Council and the Board were published, it would certainly carry much more weight than otherwise.

Dr. Sloan stated that the Council had approved the employment of part-time in-



spectors; that there remain over a thousand hospitals to be visited; that the Council will soon cover four hundred of these through their full-time inspectors, and that it will employ part-time inspectors to take care of an additional four hundred. The cost is estimated at from \$25,000.00 to \$37,500.00, this covering inspection of all departments and not merely the Department of Medicine.

Dr. Reginald Fitz inquired whether Dr. Sloan had any specific recommendations as to how much of the cost the College should be willing to contribute. President Palmer replied that the College was not in a position to make any specific commitment, because the cost has not yet been reasonably clearly determined.

Dr. Walter B. Martin presented the proposal that a hospital should contribute the cost of its inspection, just as do physicians who are taking certification board examinations, and Dr. Sloan accepted the thought as an excellent suggestion.

Dr. Fitz pointed out that the general plan is that the Council on Medical Education and Hospitals in various areas will appoint inspectors and consultants, vouched for by the College, and possibly utilizing in some manner the College Governor for that area, men who are capable of giving a fair and impartial inspection of hospitals. Such a program of inspection, with the participation of the Council, the College and the Board, will really mean something. Dr. Fitz said that it will naturally require a complicated machinery, and that the inspectors who give their time, whether it be a day or several days, should be entitled to some sort of compensation.

Dr. Fitz presented the suggestion that the College contribute \$5,000.00 to the hospital inspection program, expenditure to be made subject to the approval of the Committee on Finance.

Dr. Hugh J. Morgan thought the suggestion somewhat premature, in view of the fact that there are many facts not yet established, namely, what the program will actually cost, what its final details will be, when it will get into operation, how much the College is actually able to contribute. Dr. Morgan further pointed out that the Council on Medical Education and Hospitals is also interested in the other specialties of medicine, including surgery itself, and that the American College of Surgeons and the American Board of Surgery might have some interest in the program. He intimated that the program for Internal Medicine and its proportionate cost should be established, and the proportionate responsibilities of the Council, of the American Board of Internal Medicine and of the American College of Physicians should then be determined.

On motion by Dr. Reginald Fitz, duly seconded and carried, a resolution was adopted referring the matter to the Conference Committee on Graduate Training in Medicine, with the request that that Committee report back to the Board of Regents or to the Executive Committee of the College, concerning not only needed finances, but more specific details as suggested in the preceding discussion.

A resolution was adopted accepting Dr. LeRoy H. Sloan's report.

Another resolution, made by Dr. Ernest E. Irons, and duly seconded, was adopted, providing that the Board of Regents of the College request the American Board of Internal Medicine to explore their possibilities of contributing toward the hospital inspection program.

Dr. Maurice C. Pincoffs, as Chairman, reported for the Committee on the Alfred Stengel Memorial Award. Dr. Pincoffs reviewed the purposes and regulations of the Award, saying that it was established by the late Dr. James D. Bruce "to be awarded periodically by the President at a Convocation of the College to a Fellow, and preferably to a Fellow who has served as an Officer, Regent or Governor, who by virtue of his loyalty and service to the College deserves an honor from it that is unique. Besides loyalty and service to the College, the candidate shall have displayed an outstanding influence in maintaining and advancing the best standards in medical education, medical practice and clinical research, in perpetuating the history and traditions of medicine and medical ethics, and in upholding the dignity and the efficiency of

internal medicine in its relation to public welfare." Recipients shall be chosen by the Board of Regents at a regular meeting prior to the Convocation at which the Award is to be made. At least three and not more than five nominations shall be presented to the Board of Regents. The Committee nominated three candidates, voting was done by secret ballot and the recipient was selected, subject to announcement at the 1949 Convocation.

President Palmer then introduced a discussion and report on the program for the 30th Annual Session, New York, N. Y., March 28-April 1, 1949. He distributed the tentative list of topics and speakers. The Committee had selected a large number of topics and subjects which would be of most interest to the College members, and then proceeded to try to obtain the most able and best man to speak on each topic.

Dr. Franklin M. Hanger, General Chairman, discussed at considerable length the general plans for the 30th Annual Session, including particularly the program of panel discussions, hospital clinics and entertainment. Some new features will be introduced in the program, including having certain clinics and clinical-pathological conferences held at the hotel, although the usual hospital clinics in the hospitals will be continued in the case of convenient institutions. Dr. Hanger further discussed the exceedingly attractive program of entertainment for visiting women. He asked particularly for the advice of the Board of Regents with regard to entertaining the wives of Officers, Regents and Governors on Sunday evening, March 27, when the members of those Boards will be at their annual dinner. At the San Francisco Annual Session, the Women's Entertainment Committee paid for the expenses of such a dinner for the wives of Officers, Regents and Governors, but the current budget is inadequate to do the same at New York.

After general discussion among the Regents, it was agreed that the Women's Entertainment Committee arrange for the dinner, but that the Officers, Regents and Governors shall purchase tickets for their wives, covering the cost.

Dr. Ernest E. Irons, as Chairman of the Joint Committee for the Coördination of Medical Activities, reported that that Committee, with its related representatives, continues to meet, and discusses problems of current interest, such as veterans housing, and other matters affecting medicine and public welfare.

Dr. William D. Stroud, Treasurer, presented the following report:

"The report of the Treasurer is merely supplemental to that of the Committee on Finance. The cash balance on October 1, 1948, was as follows:

Endowment Fund .....	\$ 1,377.83
General Fund .....	74,110.11
	<hr/>
	\$75,487.94

"It is estimated that there will be some \$38,000.00 additional receipts between October first and the end of the year. The Committee on Finance will make recommendations concerning the investment of surplus funds not required for operations, and it will also report the record of security transactions since the last meeting of this Board.

"The present security holdings of the College are as follows:

	<i>Book Value</i>	<i>Market Value</i>	<i>Appreciation</i>
A. Blaine Brower Fund ....	\$ 2,500.00	\$ 2,500.00	
Endowment Fund .....	283,731.86	296,045.25	\$12,313.39
General Fund .....	176,436.22	197,139.74	20,703.52
	<hr/>	<hr/>	<hr/>
	\$462,668.08	\$495,684.99	\$33,016.91

"The annual cash income from these securities amounts to approximately \$18,500.00 per annum, and the average yield is 3.83 per cent.

"This year the Committee on Finance asked the representative who handles our account at Drexel & Co. to meet with the Committee, in order that we could discuss more in detail certain principles affecting the College investments. Of that you will hear further from the Chairman of the Committee on Finance.

"The services of Drexel & Co. appear to your Treasurer to be entirely satisfactory."

Mr. E. R. Loveland supplemented the Treasurer's Report by saying that the College had just received from Dr. A. B. Brower the second installment of \$2,500.00 on the "A. Blaine Brower Traveling Fellowship Fund."

The report of the Treasurer was by resolution accepted.

A resolution was adopted authorizing the House Committee to select chairs and other furniture for the new Second Floor Meeting Room.

Dr. A. B. Brower, Chairman, reported for the Committee on Finance, saying that representatives of our investment counselor's firm had reviewed all of the College investments and discussed same with the Committee. He reported in detail security transactions, both purchases and sales, and received the official approval of the Board of Regents on all transactions affecting the Endowment Fund, in accordance with regulations of the Board.

He stated that the Committee on Finance had further considered the matter of paying travel expenses of the Board of Governors to the Annual Sessions. It had been determined that the cost of train fare alone would amount to approximately eight thousand dollars per annum, and the Committee asked the approval of the Board of Regents to defer the matter for further study for one more year.

On the recommendation of the Committee on Finance, approved by the Board of Regents, the retirement annuity of the Executive Secretary was increased from \$200.00 to \$500.00 per month.

The Committee on Finance distributed detailed operating statements for the year 1948, including estimates of income and expenses for the balance of the year; compared appropriations and expenditures; reported them in wholly satisfactory condition and recommended their approval, which, by resolution of the Board, was granted.

Dr. Brower then presented the proposed budgets for 1949, calling for an estimated income of \$217,030.00 and an estimated expenditure of \$206,045.77, and, by resolution, the budgets were adopted.

At this point the publication of a completely revised Directory of the College was reintroduced, and a resolution was adopted approving of the project, subject to the receipt of two thousand pre-publication orders at \$4.00 per copy.

The earlier resolution concerning the contribution by the College of \$2,000.00 per annum for five years to the World Medical Association was reopened for discussion. It was opposed by some who thought it foreign to the purpose of the College, or inappropriate for other reasons. It was supported by Dr. Ernest E. Irons and Dr. Cyrus C. Sturgis, because the World Medical Association is making a survey of the standards of medical practice, medical education, training of specialists and post-graduate education, and in other ways is engaged in the study of medical scientific problems on an international plane. A resolution was finally adopted deferring the whole matter until the next Annual Session, not to turn it down definitely, but to maintain a sympathetic attitude with the expressed objectives.

Dr. Walter L. Palmer, Chairman of the Board of Governors, reminded the Board that at the San Francisco Annual Session two recommendations from the Credentials Committee—one to make certification a prerequisite for Associateship, and the other to eliminate from future College membership those engaged in the practice of the so-called allied specialties—were held in abeyance. The Minutes of the meeting were

distributed to the Board of Governors by the Executive Secretary and also published in the "ANNALS." Dr. Palmer pointed out that the personnel of the Board of Governors changes fairly rapidly, one-third of them being elected every year, or possibly in some instances at longer intervals. Dr. Palmer stated that the Board of Governors had recommended that a special committee be appointed by the President to study the matter further and before action shall be taken, the Board of Governors be allowed to hear the report and to participate in the discussion of the problem.

Dr. George Morris Piersol pointed out that the proposals were to be reviewed by the Committee on Credentials and the Executive Committee of the Board of Regents before the next Annual Session, and the Governors presumably would be present when the report is brought in for discussion.

President Walter W. Palmer announced that the Committee on Credentials would meet on February 26, 1949, at the College Headquarters, and on March 26, 1949, at New York, and that the next meeting of the Board of Regents would be held in conjunction with the Board of Governors at the Waldorf-Astoria Hotel, New York City, on March 27, 1949.

Adjournment.

Attest: E. R. LOVELAND,  
*Secretary*

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## Q FEVER—A REVIEW OF CURRENT KNOWLEDGE \*

By ROBERT J. HUEBNER, M.D., *Bethesda, Maryland*, WILLIAM L. JELLISON, Ph.D., *Hamilton, Montana*, and M. DORTHY BECK, M.A., *San Francisco, California*

Q FEVER is an acute specific, often serious, and occasionally fatal rickettsial disease of man. It is characterized by a high fever, headache and malaise and is often misdiagnosed as influenza or atypical pneumonia. It is also a disease of animals and it is the animal reservoir of the disease which is thought to be the immediate source of most human infection. Although the causative agent of Q fever, *Coxiella burneti* (= *Rickettsia burneti*) has been known and studied since 1937, Q fever, until recently, was looked upon as little more than a medical curiosity of importance to certain communities in Australia. Since 1945, however, Q fever and its causative organism have been found on an ever increasing scale in six separate countries † in three additional continents. In the United States since the spring of 1946, the disease has been found in Texas,<sup>1</sup> Illinois,<sup>2</sup> Montana,<sup>3</sup> Arizona,<sup>4</sup> and California.<sup>5, 6, 7</sup> In California, where intensive studies of Q fever are being carried out by the California State Department of Public Health and the United States Public Health Service,‡ the disease has been found in 16 counties in a period of less than one year. In Los Angeles County, where Q fever appears to be endemic, more than 300 cases and three deaths have been studied. Results of surveys including more than 3,000 persons indicated 1 per cent of the persons residing in the endemic area possess serum antibodies for Q fever.<sup>8</sup> A recent report<sup>7, 9</sup> announced that *C. burneti* was present in the raw milk supply of four of five widely separated dairies in the Los Angeles area. An extension of these studies has indicated that the raw milk of more than 60 per cent of the 63 dairies tested in the area contain sufficient quantities of *C. burneti* to readily infect guinea pigs and that more than 10 per cent of approximately 4,000 cows are infected. Fortunately, commercial pasteurization methods in rigidly controlled field tests appeared to be nearly 100 per cent effective in eliminating the infection from milk.<sup>9</sup>

\* Received for publication October 14, 1948.

† United States, Panama, Italy, Greece, Switzerland and Algeria.

‡ A Q Fever Laboratory was established at Hondo, California in September, 1947.

## HISTORY OF Q FEVER

*Q Fever in Australia:* Derrick, in 1937, reported nine cases of a new clinical entity occurring in Queensland, Australia which he named "Q fever."<sup>10</sup> The causative agent was isolated in guinea pigs from the blood of seven cases and from the urine of three cases. This agent he named *Rickettsia burneti*<sup>11</sup> after Burnet who succeeded in visualizing the organism and who first recognized it as a rickettsia.<sup>2</sup> Eight of the nine cases were slaughterhouse workers, the other a worker on sewerage construction.

The disease was rather intensively studied in Australia for the next five years during which time 118 naturally occurring cases were identified in the city of Brisbane and 34 cases in the surrounding rural areas.<sup>13</sup> One hundred and twelve of the 118 Brisbane patients were abattoir workers—among the remaining six cases were a truck driver, a carpenter, an electrician and a laundryman. Of the 34 rural cases, 26 were dairy workers, and two were meat handlers. The occupations of three were not reported but the remaining three included a butter factory employee, a fruit farmer, and a timber worker.

It seemed therefore, on the basis of case finding, that Q fever in Australia must be an occupational disease and that work with livestock, particularly cattle, was a predisposing factor to infection. In their search for sources of infection, the Australian workers succeeded in recovering the infection from two species of ticks and from the bandicoot, a native marsupial which was host to one of the species of ticks.<sup>14</sup> Although agglutinins against Q fever were demonstrated in the blood of cattle<sup>13</sup> the causative organism was not recovered from that species. There is no record that milk was ever tested.

Subcutaneous inoculation of heavily infected guinea pig tissue in calves produced an extremely mild clinical reaction.<sup>13</sup> Although *C. burneti* was recovered from the blood of each calf on one occasion (third and fourth days respectively), evidence of any considerable propagation of organisms was not obtained. Derrick attempted to trace the high prevalence of Q fever among meat and dairy workers to infected tick feces on the hides of cattle. However, no direct evidence was offered in support of this hypothesis.

*Q Fever in the United States:* In the United States the causative agent of Q fever was recovered from the tick, *Dermacentor andersoni* by Davis and Cox<sup>15</sup> in Montana several years before the illness itself was recognized. The organism named *Rickettsia diaporica* by Cox<sup>16</sup> was shown by Dyer<sup>17, 18</sup> to be similar to the causative agent of Australian Q fever.

A clinical study of a laboratory outbreak of Q fever in 1940<sup>19, 20</sup> showed that a pneumonitis was a prominent feature of the disease. However only one naturally occurring case<sup>21</sup> was reported in this country before 1946.

In 1946 two explosive outbreaks of Q fever occurred among stockyard and abattoir workers in Amarillo, Texas<sup>1</sup> and Chicago, Illinois.<sup>2</sup> Epidemiological studies of the Amarillo outbreak suggested that a single shipment of white faced heifers was responsible for the human infection whereas

sheep or calves were incriminated as probable sources of infection in the Chicago outbreak. In these and various laboratory outbreaks, just as in Australia, the mode of infection could only be surmized; however the inhalation of infected dust or droplets appeared to offer the most likely explanation. A search for serum antibodies against Q fever at Fort Worth, Texas in 1948<sup>22</sup> revealed that 8 per cent of 1,238 abattoir workers were positive for Q fever.

The first evidence that Q fever was endemic in this country was produced in the spring of 1947 when Young<sup>5</sup> discovered several cases in Los Angeles County, California. A field study by Shepard and Huebner<sup>6</sup> in that area showed that although none of the 17 cases were livestock, abattoir or dairy workers, 15 gave histories of exposure to cows either because they lived near or visited dairies. Cows on some of these dairies were found to possess serum antibodies for Q fever as did one-half of the 20 dairy workers who were tested.

Current studies in California have extended the known area of endemicity to all of Los Angeles County and to adjacent counties as well. It also has been shown that the causative agent of Q fever (*Coxiella burneti*) is abundantly present in the raw milk produced in the area. However, the rôle that infected milk may play in human infection has not been determined. Epidemiological studies that will be reported in detail later<sup>8</sup> show that two-thirds of the cases so far studied do not use raw milk nor is it used in their households. It is clear therefore that some mode of infection other than personal or household use of raw milk must be found to account for these cases. Proximity to livestock by reason of occupation or residence appears to influence the occurrence of illness.<sup>6, 8</sup> Contamination of certain environments by infected milk undoubtedly occurs but the extent of this contamination and its influence on the incidence of Q fever are unknown at this time.

*Q Fever in Italy:* In 1944 and 1945, outbreaks of Q fever occurred in U. S. Army troops in Italy and Corsica.<sup>23</sup> Epidemiological investigations indicated that transmission of Q fever from person-to-person was an unlikely mode of infection. The epidemics were largely localized to troops billeted in certain rural areas in Northern and Southern Italy. Despite the explosive outbreaks of Q fever in American troops the indigenous populations appeared to be comparatively free of similar illnesses. In Pagliana, 49 of approximately 144 American troops developed Q fever in a six month period. Similar illnesses were not observed in the 100 natives of the town; however, 16 of 28 adult residents were found to possess serum antibodies against Q fever.

*Q Fever in the Balkans:* Caminopetros<sup>24</sup> in 1943 recovered a strain of Q fever from a patient during an outbreak occurring in Athens, Greece, of an illness resembling influenza. The disease was described as endemic to the area and was known as "Balkan Grippe" to the German troops during World War II. They appeared to be highly susceptible to the disease in comparison to the local population. Q fever continues to be a problem in Greece,<sup>25, 26</sup>

where sheep and goats as well as the milk of such animals were recently reported to be infected with Q fever. It is likely that the disease exists in other Balkan countries such as Bulgaria,<sup>27</sup> and Romania.<sup>28</sup>

*Q Fever in Switzerland:* Gsell<sup>29</sup> in 1947 reported seven cases of Q fever, four from a single family in St. Gall, Switzerland. The family outbreak which occurred in a rural household included the father, his cousin, the mother and an only child less than three years of age. All had contact with cattle.

*Q Fever in Panama:* In 1945 Cheney and Geib<sup>30</sup> recovered a strain of *C. burneti* from a case of "atypical broncho-pneumonia" in Panama. The disease is now known to occur sporadically in that country.<sup>31</sup> The source or mode of human infections in Panama apparently has not been investigated.

### THE ETIOLOGICAL AGENT OF Q FEVER

*Coxiella (Rickettsia) burneti* (Derrick), the causative organism of Q fever, presents a number of unusual and interesting characteristics. On a morphological, tinctorial and cultural basis, the organism is a typical rickettsia. It requires living tissue to propagate, it stains similar to and looks like other rickettsiae. However, it distinctly differs from all other rickettsial organisms in certain biological characteristics. *C. burneti* is much more resistant to physical and chemical agents than other pathogenic rickettsiae (excepting perhaps *R. wolhynica*) and even more resistant than many vegetative bacteria.<sup>32, 33</sup> It persists for months in the tissues of infected animals<sup>34</sup>; it has distinct immunological characteristics<sup>35</sup>; it readily passes bacteria retaining filters<sup>15</sup>; and it remains viable in cell-free media for long periods at room temperature.<sup>16</sup> These and other variations from the type organism *Rickettsia prowazeki* appeared to justify the new name *Coxiella burneti*.<sup>36</sup> The various strains of *C. burneti* that have been isolated when studied in the laboratory have been found to exhibit only minor differences.<sup>37-41</sup>

### CLINICAL FEATURES

Our knowledge of the clinical manifestations of Q fever is based on 19 reports which provide a variable amount of clinical data on 625 cases. Although the outbreaks originated in six separate countries, they were found in every instance to be caused by organisms identified as *C. burneti*.

Except for an apparent absence of pneumonitis in the Australian cases, Q fever as reported from various parts of the world presents a fairly consistent clinical syndrome. This syndrome is characterized by a sudden onset, fever with relative bradycardia, headache, weakness, malaise, chilly sensations, drenching sweats and considerable variation in severity and duration. A pneumonitis which is revealed in the majority of cases examined by roentgen-ray is attended by mild cough, scanty expectoration, chest pain and minimal physical findings. Complications and sequelae are occasionally reported and five deaths occurred in the 625 cases.



Twelve reports of naturally occurring cases in which clinical findings were given on approximately 521 cases were reviewed.<sup>1b, 2, 3, 6, 10, 21, 29, 30, 42-45</sup> Unfortunately many of these studies were retrospective investigations following belated diagnosis of Q fever. Consequently accurate and detailed clinical data were not always available. In nearly all instances, the cases described in detail came from selected groups of cases (i.e., hospitalized persons or persons showing pneumonitis) and probably do not represent a true cross section of naturally occurring Q fever infections.

In those outbreaks where an attempt was made by serological or roentgen-ray surveys to pick up all cases in the exposed groups<sup>1b, 44, 46</sup> a great variation in the severity of the illnesses was reported. Ten to 25 per cent of the persons showing serological or roentgen-ray evidence of Q fever were found to have experienced extremely mild or inapparent illnesses. These findings are consistent with observations on dairy workers in Los Angeles,<sup>6</sup> packing house workers in Chicago<sup>2</sup> and in one intensively studied laboratory outbreak.<sup>46</sup> The majority of the naturally occurring cases were regarded as moderately to severely ill, whereas less than 10 per cent were seriously ill. Two deaths occurred in brothers in the outbreak in Amarillo, Texas<sup>1b</sup> and two deaths were reported from Australia.<sup>42</sup>

Seven reports of laboratory outbreaks including 104 cases were similarly reviewed.<sup>17, 19, 46-50</sup> Since most of the ill persons were under close surveillance, contemporary and more intensive clinical investigations were possible in these studies. Despite the probability that the source and mode of laboratory infections differ in major respects from natural infections there was no appreciable difference noted in the clinical patterns of the cases arising from these different sources. The four deaths among 521 natural cases may be compared to the single death<sup>19</sup> which occurred in the 104 laboratory infections.\* The following analysis of reported signs and symptoms has been based upon the total number of 625 cases which were reviewed. The average incubation period of Q fever is reported to be about 16 to 18 days; with a minimum of 13 days and a maximum of 32 days.

### CONSTITUTIONAL FEATURES

*Fever:* Except for inapparent cases, fever is the most consistent sign of the disease. The fever is characteristically remittent, occasionally intermittent, the temperature often fluctuating from somewhat above normal to 104° F. or 105° F. in a single day. However, the almost universal use of salicylates in illnesses of this nature undoubtedly influences the occurrence of such wide variations in temperature. The duration of the fever varies from one to 15 days and except in rare instances resolves by lysis over a period of several days.

*Headaches:* Headaches are recorded in more than 90 per cent of the cases.

\* The three deaths in Los Angeles County bring the total number of deaths attributed to Q fever to eight.<sup>8</sup>

They are nearly always located in the frontal area and are frequently associated with pain in the eyes.

*Pain in the Eyes:* This very prominent symptom apparently takes a number of forms; retro-orbital pain, pain on movement, pain on pressure, photophobia and conjunctival irritation.

*Chills:* Chilly sensations rather than frank rigors are described in at least 75 per cent of the cases.

*Sweating:* Drenching sweats nearly always accompany the frequent drops in temperature. In prolonged illnesses daily repetition of chills, fever and sweating leaves many patients extremely weak and dehydrated.

### SPECIFIC FEATURES

*Muscular-Skeletal:* Muscular aches and pains are frequent. Backache in some cases has been so severe as to suggest dengue. Joint pains often associated with swelling and limited motion have been reported in a small number of cases.

*Gastrointestinal System:* Anorexia is almost universally noted during the acute stage of the illness. In the severe illness considerable loss of weight occurs. Nausea and vomiting are described in about 25 per cent of the cases. Constipation is described in the Australian reports but is seldom mentioned in reports from other countries. Diarrhea on the contrary occurs more frequently.

*Cardiovascular System:* Relative bradycardia is a characteristic of the disease noted in nearly all the outbreaks. In one fatal case studied at autopsy myocardial damage was noted.<sup>51</sup> However, there is no evidence that has been presented thus far to show that persons not otherwise suffering from heart disease experience demonstrable embarrassment of cardiac function during an acute attack of Q fever. Cyanosis which is sometimes seen (5 per cent of the cases) can usually be attributed to extensive pulmonary involvement.

*Genito-Urinary System:* There are no characteristic symptoms or signs related to the genito-urinary system despite the fact that *C. burnetii* has been readily recovered from the urine.<sup>1</sup> Orchitis (three cases) and epididymitis occasionally complicate the acute illness. However, these complications are short-lived.

*Nervous System:* In severe cases, particularly in older persons, periods of disorientation have been observed. Special nursing care was for this reason required for several cases studied during an outbreak at the National Institute of Health. Neuralgic pains not uncommonly occur in the chest and in the extremities.

*Reticulo-Endothelial System:* Some enlargement of the spleen might be expected to occur in man as it does in laboratory animals. However, it is rarely reported on physical examination. Enlargements of cervical lymph

nodes have been reported only occasionally and in those instances Q fever could not definitely be held responsible.

*Skin:* A maculo-papular erythematous rash has been reported in four cases<sup>42, 46</sup>; however the absence of rash is regarded as a characteristic of Q fever which sets it apart from other rickettsial diseases.

*Respiratory System:* A pneumonitis, similar to that found in virus and atypical pneumonias, is reported in a majority of cases. In four well studied laboratory outbreaks<sup>19, 46, 49, 50</sup> more than 60 per cent of the cases showed lung lesions on roentgen-ray. A pneumonitis has become so well identified with Q fever that the roentgen-ray has been used as a case finding technic.<sup>44</sup> However, Q fever is a systemic disease of rickettsial etiology and cannot be classified simply as a pneumonitis. Serious illnesses have been produced by Q fever in which no evidence of pneumonitis could be demonstrated at any time.

The lung lesions (as seen by roentgen-ray) which may be single or multiple usually consist of irregularly shaped patches of increased density sometimes described as resembling "ground glass." There seems to be little relationship between the extent of the lesions and the severity of the illness except in those rare instances where complete consolidation of lobes occurs. The lesions tend to occur in the peribronchial and alveolar rather than the hilar regions, and more often than not are found in the lower lobes. The lung lesions occasionally clear rapidly but more frequently resolution is slow, roentgen-ray evidence often persisting after the patient returns to normal activities.

Symptoms and signs referable to the pneumonitis are repeatedly described as minimal. Respiratory distress is almost never seen but mild cyanosis is seen somewhat more frequently.

*Cough:* Cough is present in most cases. It is usually productive of only a small amount of mucoid sputum which is occasionally streaked with red blood. *C. burneti* has been recovered from the sputum.<sup>25, 46</sup>

The physical findings produced by the pulmonary lesions of Q fever are often so minimal that this point has been described as a feature of the disease. However, on repeated examinations during the peak of the illness fine râles frequently can be heard at the end of deep inspiration with sufficient clarity to localize the lesion. Dullness is not often elicited and is indicative, when present, of pleural involvement or pleural effusion as often as consolidation. *C. burneti* has been isolated from pleural fluid.<sup>50</sup> Abnormalities of voice and breath sounds are minor except in extensive consolidation.

*Upper Respiratory Signs and Symptoms:* The almost complete absence of abnormal upper respiratory findings in Q fever provides an important aid in differentiating that illness from such common illnesses as influenza, common cold, sinusitis and throat infections. Epistaxis has been reported as a minor complication.<sup>10, 46, 50</sup>

*Complications and Sequelae:* A review of the various clinical reports shows that among severe cases, complications and apparent relapses are not

uncommon. Phlebothrombosis, pleurisy, pleural effusions, arthritis, orchitis, epididymitis, esophagitis, massive intestinal hemorrhage<sup>32</sup> and decubitus ulcers have been noted during the acute stages of the illnesses.

Six patients have been recorded as having experienced relapses following apparent recovery from Q fever.<sup>42, 50</sup> The authors of this paper have witnessed one apparent relapse in southern California and one of the authors had previously observed a complete repetition of a clinical course of an illness proved to be Q fever following termination of a five day course of treatment with streptomycin.<sup>52</sup> Derrick and Burnet<sup>42</sup> reported one person who experienced a daily rise in temperature for nine weeks after onset of Q fever.

Unpublished data indicate that five of 49 laboratory infections with Q fever were followed by prolonged sequelae.<sup>52</sup> One patient whose illness was complicated by a severe phlebothrombosis has experienced during the two years subsequent to his illness, intermittent attacks of fever, pain in the legs and swelling of the ankles. Another has had persistent low back pain of undetermined cause during the same period. A third has been afflicted with persistent hiccoughs and two men over 60 have had leg pains similar to that usually described in intermittent claudication.

#### LABORATORY FEATURES

Routinely performed laboratory findings in Q fever are not distinctive. Mild albuminuria during the febrile period represents the only abnormal urinary finding. Except in the rare prolonged or complicated illness the red cell count and hemoglobin concentration remain normal. The white blood count and differential tend also to remain within normal limits but variations do not exclude Q fever from the diagnosis. A relative lymphocytosis is occasionally reported. The sedimentation rate is nearly always elevated during the acute phase of the illness and tends to return to normal early in convalescence. However, in four cases suffering apparent relapses<sup>50</sup> the sedimentation rate remained elevated after defervescence of the original illness. In one study the sedimentation rate was regarded as a reliable index of the patients' fitness for discharge from the hospital.<sup>43</sup>

All the usual blood sera agglutination tests are negative including the Weil-Felix test and tests for brucellosis and typhoid fever. Cold agglutinations are consistently negative as are complement fixation tests for influenza, psittacosis and rickettsial diseases other than Q fever.

*Laboratory Diagnosis of Q Fever:* The diagnosis of Q fever can be established with certainty only by demonstrating a substantial rise in titer in the Q fever complement fixation or agglutination tests or by recovery of the causative organism from the patient. When antigens prepared from the Henzerling<sup>30</sup> or Nine Mile strains<sup>15</sup> of *C. burneti* are used, the serological tests are both specific and sensitive. The complement fixation test performed according to the Bengtson technic<sup>53</sup> or modifications of the Kolmer technic are most generally used at this time. Unfortunately antibodies capable of

fixing complement do not appear in the blood of patients until 10 to 14 days after onset so that a serological diagnosis cannot be made during the early stages of the illness.

A positive reaction for Q fever in the complement fixation test is regarded to represent previous effective contact with *C. burneti* and a high titer associated with a previous illness consistent with what is known about the disease suggests that the illness in question is Q fever. However, antibodies are found in the serums of persons who have not been ill but who have been exposed to known sources of infection both in the laboratory and in endemic areas.<sup>2, 6, 43, 47</sup> Unpublished data from the National Institute of Health show that eight of 14 persons who had Q fever in 1940 still had detectable antibody levels in 1946. Several of that group retested in 1948 continued to show antibodies of significantly high titer.

With the exception of Rocky Mountain spotted fever, no other human illnesses have been found which produce serum components capable of giving a positive reaction in the Q fever complement fixation test. At the National Institute of Health a survey of 70 serums from cases of Rocky Mountain spotted fever, collected in 1946, showed that 10 per cent of them reacted with the Henzerling antigen in titers ranging up to 1 to 32 but not higher.<sup>54</sup>

### DIFFERENTIAL DIAGNOSIS

While it is not possible on a clinical basis alone to make a definite diagnosis of Q fever, on the same basis it is difficult to rule out the disease; particularly in known endemic areas. In such areas, however, an epidemiological history is often extremely helpful.

The clinical similarity between Q fever and many other syndromes of known and unknown etiology is repeatedly pointed out in published reports. Influenza, so-called virus and atypical pneumonias of undetermined origin, psittacosis, coccidioidomycosis present similar clinical pictures. Other rickettsial diseases can be ruled out in most instances when the rash peculiar to the specific disease fails to appear. Typhoid fever and brucellosis are diagnoses which have been considered in cases of Q fever. In areas where both brucellosis and Q fever occur, an occasional patient may have antibodies for both diseases and a final diagnosis may be extremely difficult unless animal inoculations are carried out. This situation has been encountered several times during the Southern California investigations and suggests a necessity for reviewing the diagnosis of brucellosis in some cases—particularly when a rise in titer for that disease has not been demonstrated.

### TREATMENT AND PROPHYLAXIS

Sulfonamides and penicillin have been used separately and together in treatment without perceptible effect on the course of the illness. Streptomycin has recently been reported to be of value in experimental infections with Q fever.<sup>55</sup> Clinical trials of this antibiotic that have come to the atten-

tion of the authors indicate that it may have a beneficial effect; however, controlled studies in human illness have not been reported.

Transfusions and oxygen therapy are occasionally necessary in supportive treatment of severe cases. Treatment otherwise is symptomatic, salicylates offering considerable relief of discomfort.

Aureomycin, an antibiotic derived from *Streptomyces aureofaciens*, has been found in clinical trials to benefit acute human infections with Q fever.<sup>55a, 55b</sup> Antirickettsial activity of aureomycin was first shown by Wong and Cox in laboratory studies.<sup>55c</sup> Sulfonamides and penicillin have been used separately and together in treatment with no perceptible effect on the course of the illness. Streptomycin has not borne out in more extensive clinical trials the promise suggested by earlier work.<sup>55b, 55d, 55e</sup>

A Q fever vaccine has recently been reported<sup>56</sup>; however, its use in humans has been limited to laboratory workers. Since controlled studies have not yet been done, its efficacy remains to be established.

### IMMUNITY

Second cases of Q fever have not been reported although good opportunities for reinfection exist in certain laboratory, occupational and residential groups. Serum antibodies have been shown to persist in recovered persons for 18 months<sup>57</sup> in a small series of cases. This persistence of serum antibodies for 18 months or more has been observed in some, but not all of the laboratory cases which have been tested at the National Institute of Health.<sup>54</sup> Solid resistance to reinfection with homologous or heterologous strains of Q fever is the rule among guinea pigs used for passage.

### PATHOLOGY OF Q FEVER

Detailed pathological studies were made on only one of the five fatal cases reported in the literature.<sup>51a</sup> Gross findings in this case (a man 59 years of age, who died eight days after onset) included an enlarged dilated heart which showed signs of previously established coronary lesions; consolidation, congestion and edema of the lungs and an enlarged flabby spleen. Microscopic examination of the lungs revealed bronchi, bronchioles and alveoli filled with fibrin, red blood cells and numerous cells of the mononuclear series (lymphocytes, plasma cells and large mononuclear cells). Findings in other tissues were not remarkable.

Lesions produced by inoculating monkeys<sup>51a</sup> directly into the lungs were similar to those found in the single human case above except that in the monkeys large epithelioid cells were noted in some of the alveoli of the lungs. Other tissues showed nonspecific perivascular lymphocytic infiltration which appeared to be most marked in the spleen and in lymph nodes. The spleen of one monkey and bone marrow of two monkeys showed nodules of epithelioid cells.

Mice and guinea pigs<sup>51b, 51c</sup> inoculated intraperitoneally and mice inoculated intranasally showed similar lesions in general except for the extensive pneumonias which were produced in the latter. Large spleens were consistently produced in both species regardless of the route of inoculation. A feature of the histopathology in each species was the production of granulomatous nodules 100  $\mu$  to 500  $\mu$  in diameter. These nodules were widely represented in the tissues but were most numerous in the liver, spleen, lymph nodes and the bone marrow. Giant cells and epithelioid cells were commonly found in the granulomata.

### SOURCES AND MODES OF INFECTION

The available evidence derived from studies of occurrence of Q fever in industrial and laboratory outbreaks and in endemic areas suggests that multiple sources and modes of infection may be involved.

The great majority of reported cases have occurred in adult males—this undoubtedly is influenced by the fact that most of the reports deal with occupational, laboratory and military groups. However, in one laboratory outbreak 12 of 24 female workers developed Q fever which can be compared to the 24 cases among 58 males.<sup>58</sup> Included among seven cases reported from Switzerland was a child less than three years of age.<sup>20</sup> Intensive studies from endemic areas have not been reported; however, one published report of 17 California cases included five adult women and a boy 15 years of age.<sup>6</sup> Preliminary observations in a subsequent study of the same area have confirmed the preponderance of adult males among recognized cases.<sup>8</sup>

The age and sex distribution of these cases is difficult to explain on the basis of the use of raw milk. These observations, however, do not exclude the possibility that the use of infected milk may result in Q fever but on the contrary may mean that case finding to date has been selective or that the number of persons contracting clinically apparent Q fever by this mode are not numerous. Nor do they exclude the possibility that infected milk may serve as a source of infection to specific occupational or residential groups by some mode yet to be determined.

On the basis of actual recoveries of *C. burneti*, human beings, cows, goats, sheep, bandicoots and ticks can be regarded as known natural reservoirs of Q fever. Investigations of other animals which have been shown to be susceptible for Q fever may significantly add to this list.<sup>25</sup>

*C. burneti* has been recovered from the blood, urine<sup>10</sup> and sputum<sup>25, 46</sup> of persons ill with Q fever. Despite these observations, there is no good evidence that infected persons are ever a source of other human infections, but there is much evidence to the contrary.

Five species of ticks, *Dermacentor andersoni*,<sup>15</sup> *Amblyomma americanum*,<sup>59</sup> *Dermacentor occidentalis*, *Haemaphysalis humerosa*<sup>14</sup> and *Hyalomma savignyi*<sup>60</sup> have been found naturally infected in the United States, Australia and Algeria. Except in rare instances<sup>3</sup> little evidence has been

presented to prove that any of these ticks are directly responsible for human infection. However, it appears probable that such arthropods are an important reservoir of Q fever in nature.

Cattle have been incriminated repeatedly in human infection in Australia, United States and in Switzerland. Until recently the evidence that cattle might serve as a natural reservoir and potential source of *C. burneti* consisted largely of epidemiological observations and the presence of Q fever antibodies in bovine serums. In the Los Angeles area, however, *C. burneti* has been readily and repeatedly recovered from milk. Attempts to recover the agent from blood, urine and feces of naturally infected cows have been unsuccessful.<sup>9</sup> Sheep and goats were found to be naturally infected in Greece and the milk of such animals was reported to be infectious for guinea pigs.<sup>25</sup>

The fact that another organism pathogenic for man should be found propagating in the mammary glands of cows and other milk producing animals is possibly less important than the observation that the udders of such animals have been found under natural conditions to be supporting an agent with the growth characteristics of a rickettsia and of a virus.

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# CLINICAL ASPECTS OF Q FEVER IN SOUTHERN CALIFORNIA; A STUDY OF 80 HOSPITALIZED CASES \*

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Q FEVER was first recognized in this area by Dr. Frank Young of Artesia, Los Angeles County, in May 1947. Subsequently over 300 cases of Q fever have been diagnosed and confirmed by serologic tests in Southern California.<sup>1</sup> This was the first time this disease had been diagnosed in the general population anywhere in the United States.

Two previous naturally occurring outbreaks of Q fever were known to have taken place in the United States. Both of these were of explosive onset and were limited to persons handling cattle enroute to or during slaughter. The first of these outbreaks occurred in Amarillo, Texas, in March 1946 in which 55 cases, with two deaths, were reported.<sup>2</sup> The second outbreak of 36 cases occurred in August 1946, in Chicago, Illinois.<sup>3</sup>

Of the first 250 proved cases of Q fever in Southern California, 110 were hospitalized in some 25 different hospitals during the acute phase of their illness. The records of 80 of these cases were selected for study and comprise the basis of this report. The remainder of the cases were not included either because the records were not available or were too incomplete for our purposes. The largest group (40 cases) was studied at the Los Angeles County Hospital. Eighteen of these cases were admitted during the first six months of 1948 and came under the personal observation of the author.

*Diagnosis:* The complement-fixation test for Q fever was used as the basis for diagnosis in every case. The tests were performed by the laboratories of the National Institute of Health in Bethesda, Md., and the California State Department of Public Health in Berkeley, Calif.

Two criteria for the diagnosis of Q fever were defined:

(1) A four-fold or greater rise in titer in successive blood specimens during convalescence was considered absolutely diagnostic of Q fever. Forty of our cases satisfied this criterion.

(2) A single titer of 1:32 or greater during convalescence from an acute febrile illness clinically compatible with Q fever was considered strong presumptive evidence of Q fever. Our remaining 40 cases fell into this group.

Twenty-five of the cases studied demonstrated a change in serial blood

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specimens from a negative to a positive reaction to the complement fixation test. The time in days following the onset of illness required for this change to occur is of considerable importance and may be summarized as follows:

Days After Onset of Illness	Positive	Negative	% Positive
1-6	0	17	0
7-12	29	8	78%
13-30	25	0	100%

An illustrative case is that of a 32 year old white male truck driver whose serial blood specimens showed the following titers:

Day of Illness	Complement Fixation Titer
7th	Negative
8th	1:16
9th	1:64
10th	1:128
11th	1:256
12th	1:256
14th	1:1024
25th	1:2048

These studies demonstrate the desirability of obtaining at least two blood specimens from patients suspected of having Q fever, the first drawn during the first week and the second during the third week of illness, in order to demonstrate a diagnostic rise in titer.

*Occupation and Exposure:* A history of possible exposure to potentially infectious material could be elicited in only 70 per cent of the Q fever cases. Any contact with unpasteurized milk, the handling of fertilizer, or even residence within several blocks of a dairy were considered grounds for classification as exposed personnel.

The patients studied in this series showed a wide diversity of occupations. Eighteen were employed in jobs requiring direct contact with potentially infectious material. These included eight dairy workers, three veterinarians, three slaughterhouse and meat packing plant employees, three rendering company employees, and one butcher.

The remainder of the occupations were representative of the general population and included: housewife (9 cases), salesmen (4 cases), oil well worker (3 cases), mechanic (3 cases), truck driver (3 cases), civil engineer (2 cases), chemical engineer, doctor, medical student, school girl, film technician, dress manufacturer, gasoline station attendant, telephone operator, painter, boiler inspector, policeman, fish hatchery employee, flying instructor, venetian blind manufacturer, cook and dog catcher.

It may be seen that only a minority of these cases reported close contact with cattle or their products but some type of possible exposure could be discovered by detailed questioning in a majority of cases. Approximately one-third of the cases denied any type of known exposure to suspected sources of infection.

*Age, Sex and Race:* Table 1 illustrates the age distribution of the cases studied.

TABLE I  
Sex and Race

Age	Male		Female Cauc.
	Cauc.	Negro	
1-9	1		
10-19	1		1
20-29	18	2	2
30-39	19	2	4
40-49	13	1	3
50-59	8		2
60-69	2		
70-79	1		
Totals	63	5	12

The youngest case was three years old, the oldest 75. It may be noted that 85 per cent of the cases were males and that the diagnosis was infrequent among the younger age groups. This latter observation is of special interest in view of the facts that this younger group probably represents the greatest milk consumers and that *Coxiella burneti* is present in more than half of unpasteurized milk specimens tested in this area.<sup>8</sup> Five of the patients were Negro males and an equal number of the Caucasian group were of Mexican extraction. The series is too small to draw any conclusions regarding sex or race susceptibility.

*Symptomatology:* The patients presented no distinctive nor pathognomonic symptoms, the usual symptom complex being that of a sudden onset of fever, chilly sensations, malaise, anorexia, and severe headache followed in a few days by a slight hacking cough and mild pleuritic chest pain.

The salient symptoms are presented in table 2.

TABLE II  
Frequency of Symptoms in 80 Hospitalized Cases of Q Fever

Symptoms	Number of Cases	Percentage
Sudden onset	74	92.5
Constitutional		
Fever	80	100.0
Chilliness	67	83.7
Rigors	12	15.0
Profuse perspiration	24	30.0
Malaise	75	93.7
Backache	10	12.5
Sore neck	8	10.0
Arthralgia	5	6.2
Respiratory		
Cough	50	62.5
Chest pain	29	36.2
Coryza	3	3.6
Sore throat	2	2.5
Gastrointestinal		
Anorexia	43	53.6
Nausea	26	32.5
Vomiting	21	26.2
Diarrhea	4	5.0
Abdominal pain	4	5.0

1. *Onset of illness*: This was characteristically sudden and without prodromal symptoms, many patients recalling the exact hour at which they became ill. Despite the abruptness of the onset, the patients did not feel acutely ill at first, many of them continuing work for a time. Only six patients were hospitalized during their first two days of illness but the majority had sought medical aid by the fourth day after onset. Fifty per cent of the patients in this series were hospitalized by their fourth day of illness.

2. *Fever and chills*: Fever was a complaint of every patient. True rigor occurred in but 12 instances, but almost all patients noted chilly sensations at the onset and during the first few days of illness. Drenching sweats at the height of the fever were noted by many patients, especially by those taking salicylates.

3. *Headache*: Severe and persistent headache was a very common complaint. This was the symptom most disturbing to many patients and relief could not usually be obtained with salicylates. The headache subsided following a lumbar puncture in two instances. The headache was most commonly generalized but in 12 instances was confined to the frontal area. Retro-orbital discomfort and pain on movement of the eyes was marked in only nine cases but specific inquiry revealed this symptom in a mild form in a majority of patients.

4. *Malaise*: A mild or moderate degree of malaise was present in nearly all cases. Backache and nuchal soreness were occasional complaints and transient arthralgia of one or more joints of the extremities was present in five cases.

5. *Cough*: Symptoms of infection of the upper respiratory tract were singularly lacking. They were limited to three patients who related symptoms of coryza and two who had a mild sore throat.

The majority of patients complained of cough of some degree. This often did not appear until near the end of the first week of illness and was usually of a mild non-productive character. Four patients had blood streaked sputum. None had sputum described as "rusty" or of "prune juice" appearance. The cough commonly persisted for but one or two weeks.

6. *Chest pain*: Slightly over one-third of the patients complained of chest pain of some degree. This was generally not severe and was limited to the site of pulmonary infiltration in most cases. The discomfort seemed to be pleuritic in nature, being aggravated by deep breathing or coughing, and generally lasted but a few days.

7. *Gastrointestinal symptoms*: Some degree of anorexia was almost universal and this was listed as a specific complaint in half of the patients. Nausea and vomiting were not infrequent but were usually troublesome for two or three days only, occasionally being more severe and more persistent. Transitory diarrhea shortly after the onset of illness was mentioned in four cases and an equal number of patients had mild generalized abdominal discomfort for one or two days.

1. *General appearance*: The patients were generally described as "acutely ill" upon admission to the hospital. They had moderate weakness and two were described as "prostrated." The skin was hot and flushed. Circumoral pallor was described in three instances and three patients showed evidence of moderate dehydration.

TABLE III

Frequency of Abnormal Physical Findings in 80 Hospitalized Cases of Q Fever

Physical Findings	Cases	Per Cent
Fever	80	100.0
"Acutely ill"	65	81.5
Relative bradycardia	54	67.5
Pulmonary		
Râles	47	58.7
Dullness	21	26.2
Altered breath sounds	21	26.2
Pleural friction rub	3	3.6
Meningeal		
Stiff neck	20	25.0
Stupor	14	17.5
Confusion	13	16.2
Hypoactive reflexes	8	10.0
Pharyngeal injection	30	37.5
Lymphadenopathy	13	16.2
Cardiac murmurs	8	10.0
Conjunctival injection	6	7.2
Skin rash	4	5.0
Abdominal tenderness	3	3.6
Palpable liver	3	3.6
Palpable spleen	2	2.4

2. *Fever*: The temperature upon admission to the hospital averaged 102.8° in the 80 cases studied. The average *maximum* temperature recorded during hospitalization was 103.9°. The single highest oral temperature was recorded as 106°. The temperature curve tended to show a sustained fever of 100 to 104° and lasted an average of 10 days. The duration of fever was between seven and 15 days in 90 per cent of all cases and may be summarized as follows:

Duration of Fever (Days)	Number of Cases
1	
2	
3	
4	
5.....	3
6.....	3
7.....	8
8.....	13
9.....	11
10.....	8
11.....	7
12.....	12
13.....	4
14.....	5
15.....	4
16	
17.....	1
18	
19	
20.....	1



Some fluctuation of fever was noted in most cases with sharp transitory falls in temperature associated with salicylate diaphoresis. There was no statistical correlation between either the duration of fever or the severity of illness and the age, sex, or race of the patient.

3. *Relative bradycardia*: The average pulse rate as recorded by the examining physician at the time the patient was admitted to the hospital was 97 per minute. This is somewhat lower than would be expected for the average initial temperature of 102.8°. This relative bradycardia, though absent in several cases, was quite distinct in a majority of instances and was most evident in the first few days of illness. The bradycardia did not persist after the temperature had fallen to normal.

4. *Lung findings*: Abnormal physical findings in the chest were present in somewhat over half of the cases examined. The majority of patients had pulmonary râles heard at the time of their admission to the hospital. In a few the findings were not noted until the end of the first week of illness. The râles were described as "crepitant" or as "moist" in about equal numbers of patients and were confined to relatively small areas, usually less than one half of one lung field.

The physical findings corresponded in position to the areas of infiltration noted by roentgen-ray and their location is described in the section on roentgen-ray findings.

An area of impaired resonance to percussion was noted in one-fourth of the patients. An equal number showed some type of localized alteration of the breath sounds, usually either described as "bronchial" or "impaired," a few being described as "increased."

The triad of more definite pneumonic consolidation—impaired resonance, altered breath sounds, and râles—was noted in 15 patients. One of these cases is reported in detail (case 1).

Localized transitory pleural friction rubs were noted in three patients, each of whom had complained of chest pain. None of the patients presented physical findings of a pleural effusion.

The physical findings as a rule cleared between the tenth and fourteenth days after the onset of the illness, although persistence of scattered râles was noted in some for as long as three weeks.

5. *Meningism*: Clinical evidence of meningeal irritation was noted in one-fourth of the patients and was often quite severe. Ten of these patients were sent by their private physicians into the Communicable Disease unit of the Los Angeles County Hospital with a tentative diagnosis of meningitis. Five patients with marked nuchal rigidity had no pulmonary infiltrations evident by physical examination or by roentgen-ray. Such a case of what we have come to refer to as the "meningeal form" of Q fever is reported in detail (case 2). Some degree of stupor or somnolence was noted in most of these patients and the majority showed transitory confusion and disorientation. Two patients were frankly maniacal and had to be forcibly restrained for short periods of time.

Depressed or absent deep reflexes during the acute illness were noted in the most critically ill of this group of patients. The Kernig or Brudzinski signs were positive in a few patients. Severe meningeal signs as a rule persisted for two or three days after the patient was hospitalized, rarely longer.

The 20 patients exhibiting marked meningism were all males but did not differ as a group in any other way from the remainder of the patients.

Findings by lumbar puncture will be discussed under the section on laboratory procedures.

6. *Skin rash*: Four patients were described as having a transitory macular eruption. In two, the rash was noted on the seventh and ninth days of illness, after several days of sulfadiazine therapy, and faded after the drug was discontinued.

One rash was described as "faint macules on the back and shoulders" of a 15 year old white school girl, and was noted on the third day of illness. No medication preceded this eruption and the rash was noted not to be present two days later.

"Pink macules on the chest and abdomen" of a 37 year old white male were noted on the third day of illness in another instance. No medication had been taken and this rash also faded "within a day or two."

7. *Miscellaneous findings*: *Pharyngeal congestion* of mild or moderate degree was a common finding. This was never so marked as to lead to a diagnosis of acute pharyngitis in these patients, but was usually regarded as a result of the fever and dehydration. *Herpes labialis* was noted in one patient.

*Conjunctival injection* of mild degree was present in a few patients. No exudate was noted.

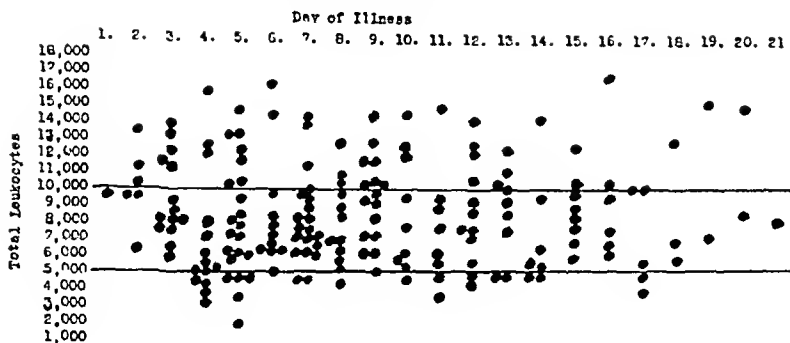
*Lymphadenopathy* was not marked in any case. Two were described as having generalized adenopathy of mild degree, one had small axillary nodes bilaterally, and 10 were described as having small, firm, non-tender anterior cervical nodes palpable. No change in the nodes was noted during the period of hospitalization of any patient.

*Cardiac murmurs* of aortic and mitral valvular disease were present in one patient with known preëxisting rheumatic heart disease. A small number of additional patients had "functional" systolic murmurs of grade 1 or 2 intensity heard best at the apex.

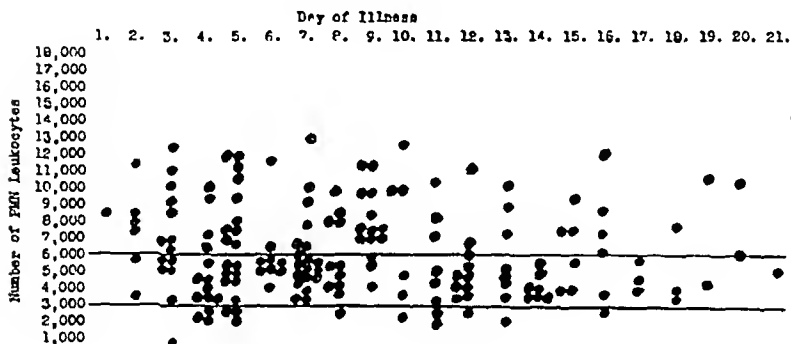
*Pericardial friction rub* was heard in one patient, a 50 year old white woman without previous cardiac disease. The rub was heard over the third interspace to the left of the sternum, was unrelated to respiration, and was heard over a seven-day period starting with the third day of illness. This patient had pneumonic infiltration in the lingular portion of the left upper lobe. Electrocardiograms showed no significant abnormality.

*Abdominal tenderness* was generalized but not severe and was associated with severe vomiting in three cases. Abdominal distention was severe and persistent for five days in one patient and was mild and transitory in another. The liver was palpable three to six centimeters below the costal margin in

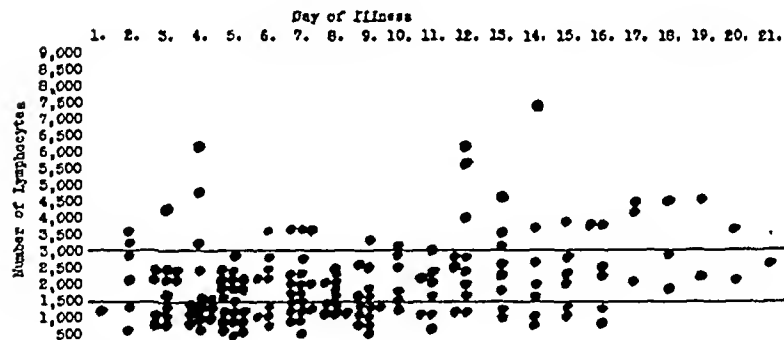
# TOTAL LEUKOCYTE COUNT



# PMN LEUKOCYTE COUNT



# LYMPHOCYTE COUNT



# MONOCYTE COUNT

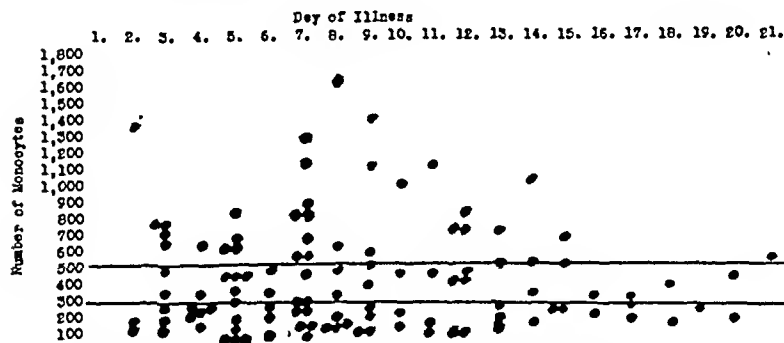


CHART 1. Absolute differential leukocyte counts calculated from 200 hemograms on 80 patients with Q fever. The counts are charted by days after the onset of illness. Horizontal lines represent usually accepted upper and lower limits of normal for each type of cell. See text for discussion.

three instances and in two cases the spleen was palpated. Liver tenderness, ascites, or jaundice was not observed in any case.

### LABORATORY PROCEDURES

1. *Blood counts*: The leukocyte counts are shown in chart 1. Variation from leukopenia to leukocytosis is evident, with a tendency to mild polymorphonuclear leukocytosis and lymphocytopenia. These findings tended to remain constant, at least during the first three weeks after the onset of illness. Eosinophilia was not noted in any case.

These findings are at variance with those reported in previous outbreaks of this disease where "relative lymphocytosis"<sup>5</sup> or "increasing leukocytosis"<sup>6</sup> during convalescence was noted.

The hemoglobin and erythrocyte determinations were within normal limits and did not change, except for the development of a mild anemia in three patients while being treated with sulfadiazine.

2. *Erythrocyte sedimentation rate*: Thirty determinations of the sedimentation rate by the Wintrobe method were performed between the third and twenty-fourth days of illness. The corrected rate was invariably elevated and ranged between 15 and 47 mm./hr. The mean corrected ESR was 30 mm./hr. and the average corrected ESR 31.5 mm./hr.

Only three determinations were performed after the first two weeks of illness, so it can not be stated how soon the sedimentation rate may be expected to return to normal. No significant decrease, however, was noted during these first two weeks.

In patients frequently exposed to both diseases, this test may be of considerable value in early differentiation of this disease from acute brucellosis, where the sedimentation rate is reported to be usually normal.<sup>7</sup>

3. *Electrocardiograms*: Electrocardiograms were taken on 12 patients in this series and showed no abnormalities indicative of myocarditis or pericarditis.

4. *Urinalyses*: Transient albuminuria during the acute febrile period was noted in 32 of the 80 cases studied. No other significant abnormality was noted.

5. *Lumbar puncture*: Twenty-four lumbar punctures were performed on 21 patients during the acute phase of their illness.

*Pressure*—the spinal fluid pressure ranged from 100 to 250 mm. of water in the 17 cases in which a pressure was recorded. The average was 165 mm. of water. The elevation of pressure in some instances was attributed to the patients' restlessness and struggles during the measurement.

*Protein*—the Pandy test was reported negative in each of 19 instances. Quantitative protein determinations ranged between 10 and 50 mg. per cent and averaged 27 mg. per cent in the nine cases in which this test was performed.

*Cells*—cell counts performed in 23 instances were normal in every case

and ranged from 0 to 10 lymphocytes per cu. mm. The average cell count was 2 lymphocytes.

*Chlorides*—spinal chlorides were recorded in 12 cases and ranged from 600 to 750 mg. per cent. The average was 690. All but three were below the accepted normal values of 725 to 750 mg. per cent.

*Sugar*—the spinal sugar ranged from 56 to 126 mg. per cent, averaging 81 mg. per cent in the six cases in which this determination was made.

*Wassermann*—the spinal Wassermann was negative in five cases and positive in one. (See blood Wassermann.)

6. *Blood agglutination tests: Typhoid and paratyphoid* agglutinations were negative, in each of 54 determinations.

*Brucella* agglutinations were negative in 56 instances and positive in one (case 2).

*OX-19* agglutinations were negative in each of 55 instances.

*Cold* agglutinins were present in a titer of 1:32 in one case, 1:8 in another and were negative in 20 cases of convalescent Q fever.

*Heterophile* agglutinations were negative in each of 15 instances.

*Tularemia* agglutinations were negative in two patients.

7. *Serologic tests for syphilis:* The Kahn tests was negative in 45 cases, the Wassermann in 31, Kline in 5, Kolmer in 3. Two patients had positive Wassermann and Kahn tests.

One was a 42 year old Negro male laborer who had a positive Wassermann and Kahn on two occasions and a positive spinal Wassermann. He was not treated for syphilis but was advised to return to the out-patient clinic. He failed to keep his appointment and it has been impossible to contact him for follow-up study.

The second patient was a 38 year old white male meat inspector in a packing plant, whose private physician has reported that his serologic tests for syphilis were still positive in high titer two months after recovery from Q fever and who is now receiving antiluetic therapy.

8. *Roentgen-rays:* Of the 80 patients studied, 77 had chest roentgenograms taken during the first few days of illness. A total of 162 films were studied in this group. The findings are summarized in table 4.

The predominant lesion was a uniform segmental or lobar consolidation of variable density. Only occasionally was there a patchy or confluent type

TABLE IV  
Location of Pneumonic Infiltrations as Seen by X-Ray  
in 77 Hospitalized Patients with Q Fever

Location	Number of Patients	Per Cent
Left lung	33	42.8
Right lung	27	35.1
Bilateral	5	6.5
Lower lobes	32	41.4
Mid-lung fields	20	26.0
Upper lobes	13	17.0
No infiltration	12	15.6

of infiltration. Multiple areas of involvement were infrequent. There was no significant correlation between the presence or extent of pulmonary infiltration and the clinical severity of illness.

In several instances, increase in the extent of the area of the pneumonic process during the first week of illness was noted. Pleural reactions adjacent to the areas of consolidation were fairly frequent, but frank pleural effusion was not noted. Generalized vascular or hilar accentuation was notably absent. There was no evidence of mediastinal or hilar lymphadenopathy.

The rate of resolution was quite variable but was often prolonged for several weeks.

### RECOVERY

The majority of patients felt entirely well and were able to return to work within a short time after discharge from the hospital. A few suffered a more prolonged convalescence, continuing to complain of anorexia, asthenia, and mild malaise for some months after apparent clinical recovery from the acute infection.

One patient, a 28 year old male dairyworker, with a complicating pneumoconiosis from previous pottery work employment continued to run a low grade fever for several weeks after the onset of his Q fever.

Two patients, aged three and 45 years, developed relapses six and eight weeks respectively after the acute infection. In each case the patient was "not entirely well" after the first episode and had only a few days of fever during the second hospitalization.

### THERAPY

Penicillin was used in the treatment of 61 of the cases studied, without evidence of any alteration in the clinical course of the disease. Sulfonamides were used in 23 cases, singly or in combination with penicillin, also without apparent benefit. Roentgen-ray therapy of the chest was used in five cases in three daily doses of 100 to 150 r each. Treatment was started between the fifth and seventh days of illness in every case. No obvious change in the patients' course occurred and the total duration of fever in every case was slightly longer than the 10-day average for the total group of patients.

Para-aminobenzoic acid, in doses of one to two grams every two hours, did not appear to alter the course of the three patients in which it was tried.

Streptomycin has been reported to be effective in preventing growth of *Coxiella burnetii* in the yolk sac of the fertile hen's egg and may be life-saving in experimentally inoculated guinea pigs.<sup>8</sup> Eight patients in this series were treated with streptomycin, receiving an average total dose of 11 grams. Treatment was started between the sixth and the tenth days after the onset of illness in every instance. No definite improvement could be ascribed to the drug in any case and the fever persisted an average of six days after therapy was started. It should be mentioned that the patients treated with

streptomycin were the most critically ill patients; the mortality rate for untreated Q fever is only 1 or 2 per cent, and this series is small, making any evaluation of therapy impossible in this case.

Aureomycin appears to be the most effective therapeutic agent in the treatment of Q fever.<sup>9</sup> This drug was not available for use prior to June 1948, so was used in none of the cases in this series.

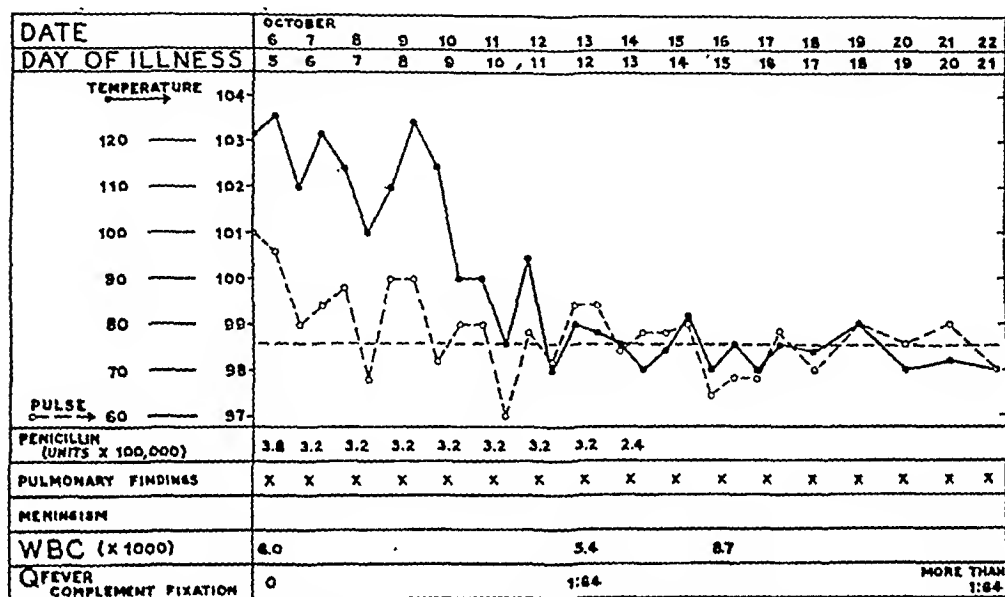


FIG. 1. Patient (case 1) with Q fever manifested by findings of "atypical pneumonia."

*Case 1.* This patient was a 55 year old white male night watchman from whom no history of contact with possibly infectious material could be elicited. He had suddenly become ill October 2, 1947, with fever and chills, severe generalized headache, nausea and vomiting, non-productive cough, and sharp pleuritic pain in the right upper anterior chest. No hemoptysis or dyspnea was noted. He had noted drenching sweats starting the day following the onset of his fever.

He was admitted to the pneumonia ward of the Los Angeles County Hospital October 6, 1947. The patient appeared acutely ill with a temperature of 103.2°, pulse rate 100, respiratory rate 24, and blood pressure of 125 mm. of mercury systolic and 75 mm. diastolic. There was no skin rash and the neck was not stiff. Small, firm, non-tender axillary lymph nodes were palpable bilaterally. Examination of the chest revealed impaired resonance and "medium moist crackling râles" over the right anterior chest. No friction rub was heard.

The heart was not enlarged and no murmurs were heard. The spleen was not palpable and the remainder of the physical and neurological examinations was negative.

A chest x-ray taken October 6 showed right middle lobe pneumonia (figure 2). Blood counts showed no anemia and the leukocyte counts were within normal limits. Agglutination for typhoid, paratyphoid A and B, brucella, and OX 19 were negative on October 7 and October 13. Four blood cultures were negative. The blood Wassermann and Kahn tests were negative.

The complement fixation test for Q fever was negative on October 6, positive in dilutions of 1:64 on October 13, and positive in all dilutions tested on October 22.

The patient received injections of penicillin, 40,000 units every three hours, without apparent clinical improvement. He did not continue to vomit following his hospitalization and the headache subsided within a few days. The lungs were noted to be resonant on October 14 but moist râles persisted to October 22 when he was discharged from the hospital.

Reëxamination of the patient on November 10 revealed him to be afebrile and asymptomatic. The lungs were clear and no abnormal physical findings were noted. A repeat chest roentgen-ray at the time showed almost complete resolution of the previously described infiltration.

*Comment:* This patient illustrates the characteristic abrupt onset of illness four days before hospitalization. He had pleuritic chest pain and cough and presented the physical findings of pneumonic consolidation of the right middle lobe. Laboratory findings were not distinctive other than a diagnostic rise in titer to the Q fever complement fixation test. No response was noted to penicillin therapy by the eleventh day after onset. The roentgen-ray showed almost complete clearing of the right middle lobe infiltration seven weeks after he first became ill.

This syndrome of "atypical pneumonia" was the one most often encountered in the series of patients studied. Approximately one half of the hos-



FIG. 2. Roentgenograms of the chest (case 1) taken on the fifth and fortieth days after the onset of illness.



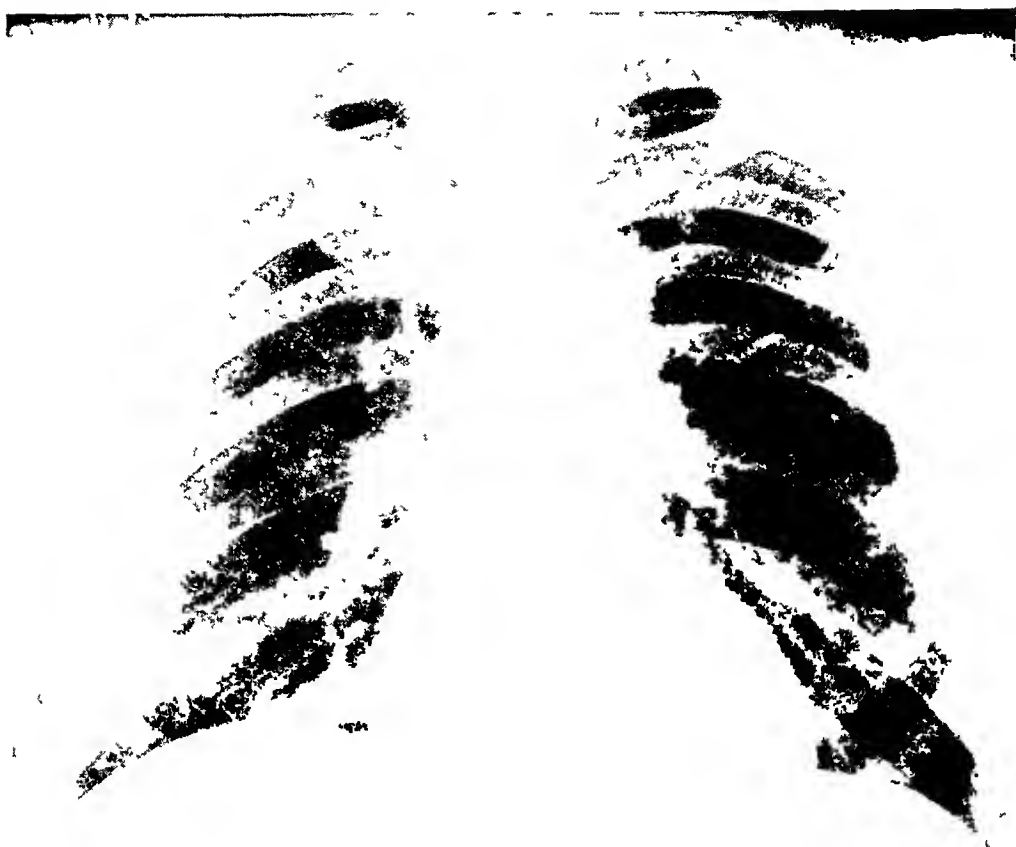


FIG. 2. (Continued.)

pitalized patients had initial tentative diagnoses of primary atypical pneumonia.

*Case 2.* This patient was a 37 year old Negro male employee of 17 years' service in a local rendering company who was admitted to the Los Angeles County Hospital March 30, 1948. He had been well until March 26, when he had suddenly become ill with fever, malaise, chilly sensations, severe frontal headache, and a slight non-productive cough. There was a mild discomfort in the right anterior chest which was aggravated by inspiration. There was no history of past illness suggestive of chronic brucellosis.

Physical examination revealed an acutely ill adult with a temperature of 101.2° and a pulse rate of 80. The respiratory rate was 20 and the blood pressure 95 mm. of mercury systolic and 55 mm. diastolic. There was no skin rash and the neck was not stiff. The chest was resonant and no râles or friction rubs were heard. The heart was not enlarged and no murmurs were heard. The spleen was not palpable and there was no lymph node enlargement. The reflexes were physiological.

The cough and chest pain subsided within two days but the severe headache and fever persisted. On April 3, a marked change in the patient's condition had occurred. He was extremely lethargic and confused. His neck was rigid and the deep reflexes were all absent. A chest roentgen-ray taken at this time was entirely negative. A lumbar puncture was performed and revealed clear colorless fluid with a pressure of 140 mm. of water. The Pandy test was negative and microscopic examination revealed no cells.

Four blood cultures were negative for brucella and cultures of the urine and sternal marrow were negative. Typhoid, paratyphoid, OX 19 and cold agglutinations were negative on April 3. Cold agglutination tests were repeated April 10 and were negative. The blood Wassermann and Kahn were negative. An electrocardiogram taken April 3 was normal.

A second chest x-ray was taken April 14 and still showed no abnormality. Remaining laboratory studies and therapy are outlined in figure 1.

The patient still appeared critically ill but seemed somewhat improved by April 5. The deep reflexes were again active on April 6 and the headache and stiffness of the neck had subsided by April 7.

The patient was left with some temporary residual weakness but was entirely asymptomatic by April 20, when he was discharged from the hospital.

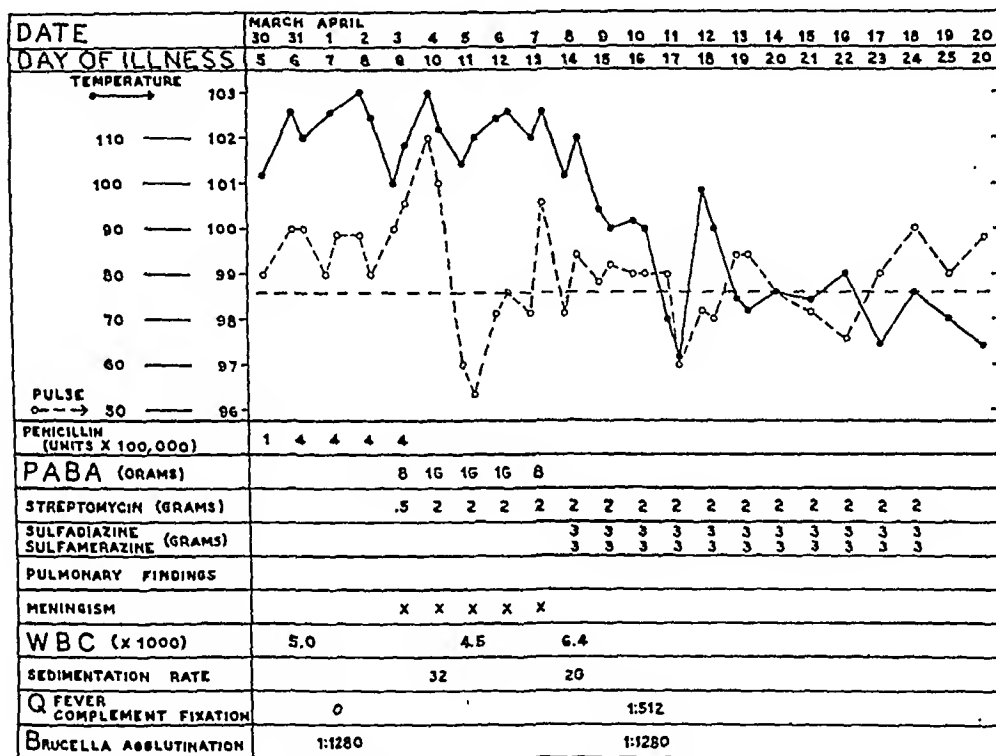


FIG. 3. Patient (case 2) with Q fever manifested by findings of meningism.

*Comment:* This patient is representative of a group of cases comprising about one fourth of the cases studied. These patients are all characterized by severe but transitory meningism without clinical evidence of pneumonia. (It should be emphasized that most of this group did show some pneumonic infiltration by roentgen-ray, however, and the patient discussed was exceptional in that repeated roentgen-rays were negative.) Another unusual feature of this case was the positive agglutination for brucella. The unchanging titers and the negative blood, urine and bone marrow cultures suggest that the patient had had sub-clinical brucellosis prior to the onset of his Q fever.

The abrupt onset of illness, frontal headache, bradycardia, pleuritic pain, meningism, and elevated sedimentation rate were so characteristic of Q fever that we felt justified in a therapeutic trial of para-aminobenzoic acid (16 grams per day) and streptomycin (2 grams per day). This medication was started April 3 and continued to April 7 without definite demonstrable effect. On this date the para-aminobenzoic acid was replaced with sulfadiazine and sulfamerazine (3 grams of each per day) and the combined sulfonamide-streptomycin therapy continued through April 18. The diagnostic rise in titer of the Q fever complement fixation test was noted by April 10.

The temperature first fell to normal on April 11 (the seventeenth day of illness), rose briefly the following day and then remained normal. It is impossible to attribute recovery in this case to any of the several therapeutic agents employed.

*Case 3.* This patient was a 22 year old white male employee of the County animal shelter who was admitted to the Los Angeles County Hospital, July 5, 1948. His work brought him in frequent contact with animals of all sorts including cows and goats, but he denied drinking unpasteurized milk. He had been in good health until July 3 when he had first noted slight fever and a sore throat. The following day he developed a very severe frontal headache, had increased fever and a severe shaking chill followed by drenching perspiration. The day of admission he had two additional chills, moderate backache and generalized malaise, slight retro-ocular discomfort and mild epigastric pain. There was no nausea or vomiting and he denied cough or chest pain.

Three years previously he had a febrile illness while stationed with the Navy in the South Pacific area. He stated that blood smears were negative for malaria at that time and no subsequent episodes of fever had ever occurred.

Physical examination revealed an acutely ill young man complaining bitterly of headache, with a temperature of 101°, pulse rate of 92, respirations 26, and blood pressure of 116/70. There was no skin rash and the neck was not stiff. The pharynx appeared mildly injected and slight enlargement of the anterior and posterior cervical axillary lymph nodes was noted. The chest was resonant and no râles or friction rubs were heard. The heart was not enlarged and there were no murmurs.

The abdomen was not distended. The spleen was palpable 4 cm. below the left costal margin and was firm and rather tender. No other abdominal organs were palpable. The reflexes were physiological.

Repeated examinations of thick and thin blood smears by the parasitology laboratory failed to reveal Plasmodia. Repeated stained blood smears showed no cells considered diagnostic of infectious mononucleosis. Heterophile agglutinations were negative on July 6 and July 12. Agglutinations for typhoid, paratyphoid A and B, OX 19, brucella and *P. tularensis* were negative. Six blood cultures were negative. The blood Wassermann and Kahn tests were negative. An electrocardiogram taken July 6 was normal.

Roentgen-rays of the chest, both antero-posterior and lateral views, were negative on July 6.

The complement fixation test for Q fever was negative on July 6 and positive in dilutions of 1:256 on July 12.

The patient received symptomatic therapy only and the headache and fever subsided within a few days. The spleen remained palpably enlarged for one week.

Reexamination three weeks later revealed the patient to be afebrile and asymptomatic and to have no abnormal physical findings.

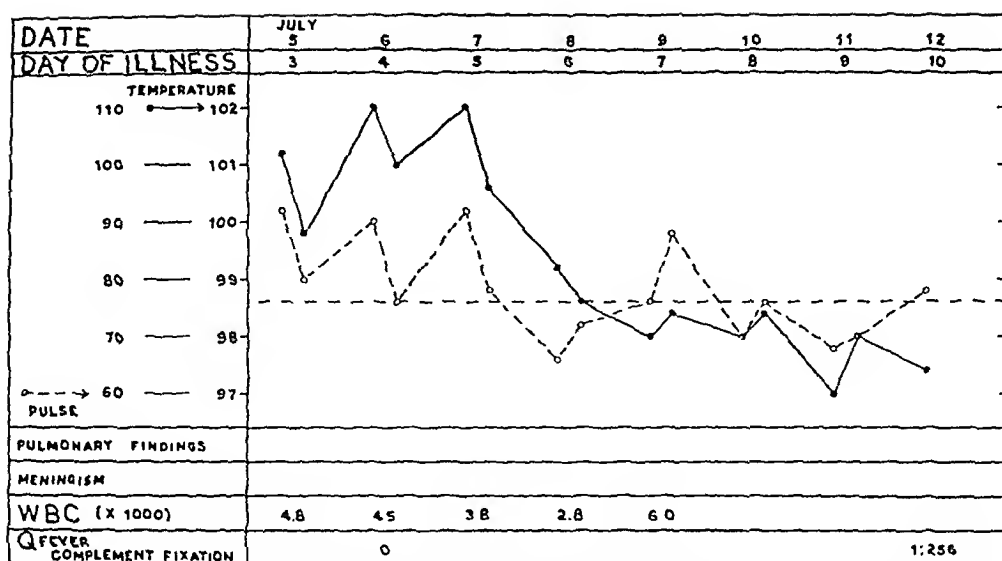


FIG. 4. Patient (case 3) with Q fever manifested by systemic symptoms without pulmonary or meningeal findings.

*Comment:* This patient represents a case of Q fever with evident constitutional effects of his disease, but without clinical evidence of either pulmonary or meningeal involvement.

Approximately one fourth of all hospitalized cases presented this picture of fever without localizing findings by physical examination; however, most of this group did reveal unsuspected pulmonary infiltrations by roentgen-ray.

Splenomegaly of a degree to render palpable this organ was uncommon in this outbreak of Q fever, as was the lymphadenopathy demonstrated by this patient.

The majority of this group received an initial tentative classification of "influenzal syndrome" pending results of laboratory tests such as the complement fixation test which, as in this case, established the diagnosis of Q fever.

### SUMMARY

Q fever has been found to be occurring in the general population of Southern California. Eighty hospitalized cases were selected for clinical study on the basis of completeness and availability of records. Of this number, one-third denied even remote exposure to cattle or unpasteurized milk. Eighty per cent of the cases were adult males.

The most common symptom complex was that of a sudden onset of fever, chilly sensations, malaise, anorexia, and severe headache followed in a few days by a slight hacking cough and mild pleuritic chest pain. The patients were febrile, had a relative bradycardia, and appeared acutely ill. Localizing physical findings were indicative of pneumonia or meningism or were entirely lacking. Illustrative case histories are presented. The fever persisted between seven and 15 days and then subsided by lysis. Convalescence was

apid and complete as a rule but was occasionally prolonged. Two patients had mild relapses requiring re-hospitalization. The results of therapy with penicillin, sulfonamides, roentgen-ray, streptomycin, and p-aminobenzoic acid were inconclusive. Aureomycin was not used in the treatment of any patients in this group.

The blood counts were variable but commonly showed a mild polymorphonuclear leukocytosis and lymphocytopenia. The erythrocyte sedimentation rate was elevated in every case. The spinal fluid was normal except for some increase in pressure and slightly decreased chloride content. OX-19 and cold agglutination tests were negative. "False positive" serologic tests for syphilis were not noted. Chest roentgenograms showed infiltrations in the majority of cases, usually a uniform segmental or lobar consolidation.

The complement fixation test for Q fever was found to become positive during the second week of illness. In every case the final diagnosis of Q fever was dependent upon this test.

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# COUGH AS A SYMPTOM OF CARDIOVASCULAR DISEASE \*

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COUGH is such a common complaint that it often attracts but little attention. This is particularly true when the cough is nonproductive and when there is no hoarseness, fever, or chest pain. It is easy to understand, therefore, how cough as a symptom may be neglected frequently in patients with cardiovascular disease in contrast to more definitive and impressive symptoms such as shortness of breath and chest or arm pain. This seems generally to be the case, since there are only a few reports pertaining to cough as a symptom in cardiovascular disease, and the majority of these have originated on the European continent.

In the past few years we have observed several patients with various types of cardiovascular disorders in which cough was an early and important but generally neglected symptom. However, with careful evaluation of the history in each of these cases the importance of the symptom of cough was recognized usually because of its prompt subsidence following adequate therapy. The following representative cases are presented.

## RHEUMATIC HEART DISEASE WITH MITRAL STENOSIS

*Case 1.* A 38 year old laborer was first seen in the hospital in January 1937 because of cough and hemoptysis. Seven weeks before entry he had developed a cough which at first was nonproductive. Later he coughed up one to two tablespoons of bright red blood, and within two weeks he was raising blood once or twice a day. At about this time he noticed the onset of shortness of breath when he climbed stairs.

Physical examination revealed that the heart was normal in size by both physical and roentgen-ray examination. The rhythm was regular at 86 beats per minute. Auscultation, however, revealed an apical systolic murmur of moderate intensity followed by a moderate, low-pitched, rumbling diastolic murmur. Rest in bed and digitalization were prescribed.

He did well without further cough or bleeding until October 1938, when he again developed a cough, following an upper respiratory infection, which resulted in his raising blood on several occasions. He also noticed some dyspnea upon exertion and was awakened several times at night out of a sound sleep by cough and shortness of breath.

Physical examination at this time was unchanged. The blood pressure measured 120 mm. of mercury systolic and 60 mm. diastolic. The corrected sedimentation rate was rapid (1 mm. fall per minute). The electrocardiogram is shown in figure 1A. Blood and urine studies at the time were not remarkable.

The patient was again admitted to the hospital one month later because of a recurrence of the cough, followed two days after entry by recurrent gross hemoptysis. The vital capacity of the lungs at this time measured 3.6 liters and his venous pressure

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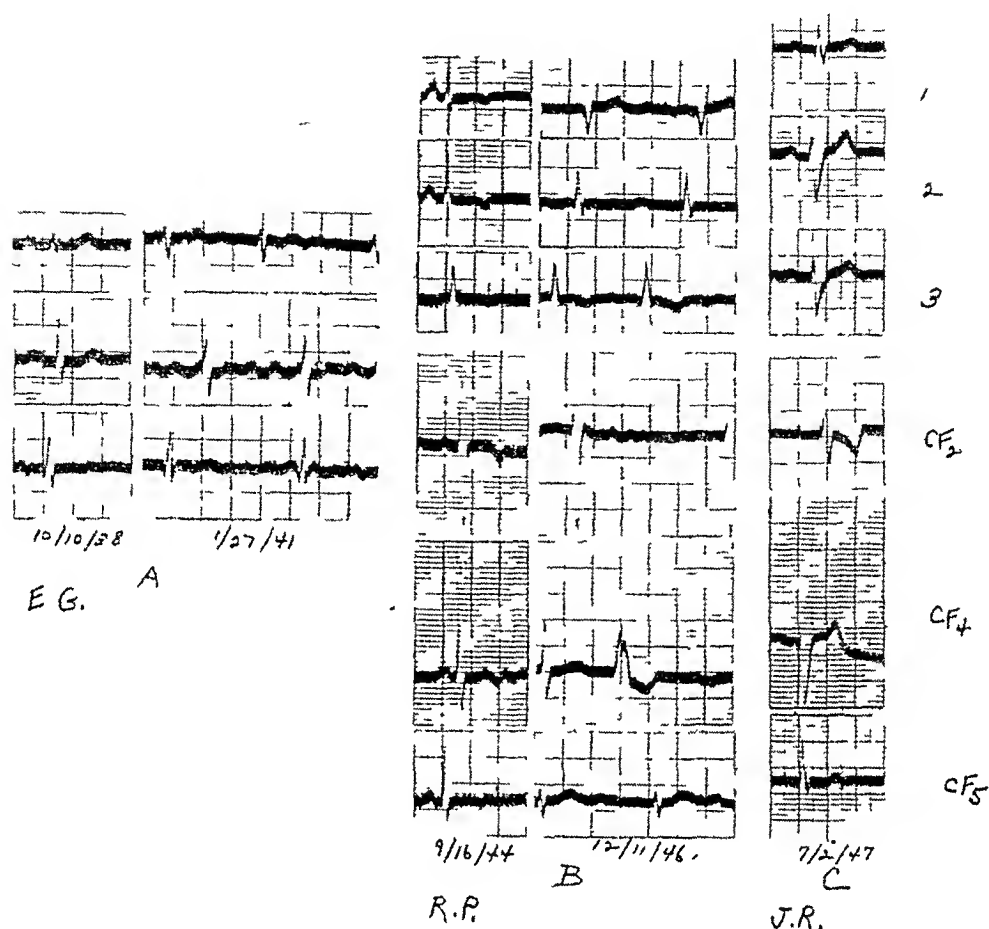


FIG. 1.

A. The electrocardiogram of Case 1, demonstrating a normal axis and wide P-waves in October 1938. By January 1941 auricular fibrillation and some right axis deviation had developed.

B. The electrocardiogram of Case 8, illustrating inversion of the T-waves in September 1944. In December 1946 much right axis deviation and auricular fibrillation are evident.

C. The electrocardiogram of Case 10 reveals a QRS interval of 0.10 second and inversion of the T-wave in Lead CF<sub>2</sub>.

was 7.5 cm. He was given supplementary digitalis for one week, 0.1 gram per day, and was discharged improved after two weeks.

In March 1939 the cough and increasing dyspnea returned, followed by frank hemoptysis. He was readmitted to the hospital at this time. Venous pressure measured 13 cm. of water, and 400 c.c. of blood were removed with some improvement. He was followed in the Cardiac Clinic where he got along well. The murmurs remained the same, and the pulmonary second sound was thought to be not abnormally loud.

In January 1941 the patient was again in the hospital because of pain in the right kidney region, which was interpreted as probable infarction of the right kidney. He had noted the onset of rapid, irregular heart action about four weeks before this, when the electrocardiogram demonstrated in figure 1A was taken. Following this episode he had developed signs of considerable congestive heart failure and had required periodic mercurial diuresis.

Since 1942 the patient has been followed periodically and has been maintained on digitalis and ammonium chloride, in addition to a low sodium intake. He has continued to have repeated small hemoptyses with some intermingled cough. A venesection about every three months has seemed helpful.

The patient was last seen in the hospital in April 1947, because of increasing cough and dyspnea over a period of two weeks. At this time his heart was found to be enlarged and the pulmonary second sound was accentuated. There was a Grade 3 apical systolic murmur followed by a moderately loud, low-pitched diastolic rumble. The rhythm was totally irregular. During the course of one week seven pounds of edema fluid were cleared, and the patient felt considerably improved.

He has since led a sedentary existence, unable to work. The cough continues periodically, especially at night, and he raises a variable amount of blood.

Cough and hemoptysis were early symptoms in the course of this patient's heart disease and appeared before significant signs of heart failure.

*Case 2.* A 34 year old mother of six children entered the hospital on June 25, 1947, complaining of cough and shortness of breath. The patient had first noted some nervousness three years before entry, but this had not been severe and had subsided after a few months. One year before entry she had noted fatigue, some palpitation of her heart, and slight dyspnea on exertion. For six months before entry she had had a mild, nonproductive cough which seemed to be progressive and during the month prior to admission had caused her difficulty in sleeping at night. At this time she had consulted her physician, who told her that she had bronchitis, for which he prescribed some cough medicine, with no effect. The patient's symptoms continued and one week before entry she again saw her physician, who noted that the thyroid gland was enlarged and referred her to the hospital. Three days before entry she vomited following a severe paroxysm of coughing. The past history revealed that she had had chorea at the age of six.

Physical examination revealed a nervous, hyperactive female. The skin was warm and moist, and the eyes showed a widening of the palpebral fissures and a definite lag. There was a mild tremor of the hands. The thyroid was found to be three times normal size and symmetrically enlarged. Examination of the chest revealed no râles, and the neck veins were not engorged. The heart was found to be enlarged on physical examination. The rhythm was regular, and the rate was rapid, varying between 100 and 140 beats per minute. The first sound at the apex was accentuated, as was the pulmonary second sound. There was a characteristic apical diastolic rumbling murmur with very marked presystolic accentuation. No systolic murmur was heard. The blood pressure was 135 mm. of mercury systolic and 60 mm. diastolic. The liver edge was found to be 4 cm. below the right costal border. The venous pressure measured 15 cm. of water.

The heart was enlarged by roentgen-ray, measuring 13.4 cm. in diameter with an internal thoracic diameter of 23.5 cm., with enlargement of the left auricle. An electrocardiogram demonstrated sinus tachycardia at a rate of 135, with a moderate degree of right axis deviation and slight depression of the S-T segments in Leads II and III. The initial basal metabolic rate was plus 76; this fell to plus 12 in the course of three weeks on iodine and thiouracil therapy.

The patient was given 4 grams of ammonium chloride a day and was placed on a low-sodium diet. No digitalis was given. She improved quite rapidly and her weight decreased by six pounds during the first five days in the hospital, a reduction which was attributed to loss of edema fluid. The patient's cough disappeared within three days after entry and she was able to sleep comfortably at night. One week after entry her venous pressure was 9 cm. of water.



This patient had symptoms suggesting thyrotoxicosis for a period of at least one year and possibly some decrease in cardiac reserve during this period of time. However, the outstanding symptom during the last six months of her illness, particularly the last month, was a cough at times paroxysmal and unusually bothersome at night. The cough subsided promptly with the disappearance of the congestive heart failure without the aid of digitalis. It seems evident that the cough was not due to the thyroid enlargement, in view of its subsidence without removal of the gland.

### HYPERTENSIVE AND CORONARY HEART DISEASE

*Case 3.* A 74 year old executive was first seen by us in January 1946. He had a known history of hypertension for six years. Six months before he was seen the patient had first noticed the onset of cough. He had been kept in bed for a few days and the cough had subsided temporarily. However, he had continued to cough intermittently, and six days before being seen he had a severe fit of coughing, with considerable blood-tinged sputum, during the night. The cough lasted all night, and he was obliged to sit up to alleviate it. The next morning his doctor found him fairly comfortable but kept him in bed. He then remained quite asymptomatic until the night before he was seen by us, when he had another paroxysm of coughing associated with dyspnea and blood-tinged sputum. This continued throughout the night and was accompanied by considerable wheezing with shortness of breath. Increase in the heart rate after coughing was noted.

Physical examination revealed no pulsation of the cervical veins, and the breathing was normal. The heart was found to be slightly enlarged. An apical diastolic gallop rhythm was easily heard. The blood pressure was 200 mm. of mercury systolic, 110 mm. diastolic. The pulse was regular at 72. No murmurs were heard, and the lungs were found to be clear. The liver was not palpable, and there was no peripheral edema. Fluoroscopic examination revealed slight enlargement of the heart, which had a transverse diameter of 12.7 cm. with an internal thoracic diameter of 25.9 cm. by orthodiagram. The hilus shadows were somewhat prominent, but the lungs appeared clear. An electrocardiogram demonstrated normal rhythm at a rate of 90 with left bundle branch block.

The patient was placed upon digitalis, ammonium chloride, a low-sodium diet, and periodic mercurial diuresis. Within four days he had improved considerably and his cough had disappeared while he was at rest in bed. No evidence was found to suggest thrombophlebitis in the legs, as a possible source for pulmonary embolism and infarction. He complained of some weakness after he was mobilized but noticed no return of the cough. During the first week he had lost six pounds in weight. He returned to part-time work but in two months had noted the return of his cough with some dyspnea. The cough was particularly bothersome at night, and during paroxysms of coughing he would raise blood-tinged sputum. At this time he was hospitalized and an intensive search was made for possible signs of thrombophlebitis or pulmonary infarction but there was no evidence of such.

In spite of the restricted sodium intake, ammonium chloride, and digitalis, the patient continued to have recurrence of cough and shortness of breath every four to eight weeks, necessitating mercurial diuresis. Cough seemed to be his first symptom of recurrent pulmonary congestion. He never developed evidence of significant right-sided failure, and his weight fluctuated not more than four to six pounds.

The patient continued with his part-time work, but he did at times notice nervousness. It seemed also that his cough was aggravated by nervous tension. During the following year examination of the heart varied little except for some increase in its

enlargement (it measured 13.8 cm. in transverse diameter by orthodiagram) and some increase in prominence of the lung hilus shadows. The apical diastolic gallop rhythm increased in intensity. When seen in July 1947 his only trouble was his cough, for which he received mercurial diuretics effectively every week or two. His cough had been more bothersome at night and during the morning shortly after arising.

*Case 4.* A 60 year old housewife entered the hospital because of cough and breathlessness. For seven years she had had a history of elevated blood pressure and of substernal tightness on effort. One year before entry she was found to have auricular fibrillation, with a ventricular rate of 160, and was given digitalis. Five months before entry she had her gall-bladder removed because of stones. Two months before entry she had noticed some shortness of breath upon dressing in the morning, although it was not particularly bothersome during the day and no orthopnea was present. For four weeks she had had a dry, persistent, nonproductive cough which bothered her particularly after effort and which for two weeks had been considerably worse. Because of the cough and breathlessness at night she had had great difficulty in sleeping.

Physical examination revealed a woman in moderate respiratory distress. The neck veins were distended and a venous pulse was visible in the neck. The heart was enlarged and the rhythm was totally irregular, with an apical rate of 96. An apical diastolic gallop rhythm was present. The pulmonary second sound was accentuated, and there was a Grade 2 apical systolic murmur. The blood pressure was 160 mm. of mercury systolic and 100 mm. diastolic. The lungs were clear. The liver descended four fingers'-breadth on deep inspiration. No dependent edema was apparent. The vital capacity of the lungs on entry was 1.2 liters. The urine contained 2 plus albumin. A chest film revealed some haziness in the right lung field just above the diaphragm. The electrocardiogram showed auricular fibrillation at a ventricular rate of about 85, slight depression of the S-T segments, and low T-waves in Leads I, II, and III. On the tenth hospital day a pleural friction rub was heard over the right chest posteriorly; this disappeared after three days.

The patient was placed on an increased ration of digitalis, together with ammonium chloride, and was given three injections of a mercurial diuretic. During the first week in the hospital she lost 13 pounds of weight, during which time the cough disappeared and her respiratory distress subsided. After two weeks she was discharged completely free of cough and shortness of breath and untroubled by insomnia.

This case illustrates the importance of cough as a complication of left ventricular failure. The patient noted some shortness of breath on effort before the cough appeared, but the cough was present before orthopnea and insomnia developed and doubtless was an aggravating factor in this respect. It seems quite probable that pulmonary infarction with pleurisy was the chief cause of the cough. The possibility of such a precipitating factor should always be explored.

#### CARDIOVASCULAR SYPHILIS

*Case 5.* A 54 year old housewife entered the Out Patient Department of the Massachusetts General Hospital in August 1938, complaining of a non-productive cough of 12 months' duration. Four years before entry she had first noted a slight pulsation in the right anterior chest. This, however, was not bothersome except for a period of six months in 1937, at which time she had occasional pain beneath the right clavicle in the region of the pulsation; the pain disappeared spontaneously. Twelve months before entry she had begun to cough, and the cough had grown

progressively worse. Shortly after its onset the patient had two attacks of dyspnea at night which awakened her from a sound sleep and forced her to get out of bed to breathe. However, there had been no recurrence of these attacks of dyspnea, nor had she noticed any appreciable dyspnea on exertion.

Physical examination revealed a well developed female in no distress. Her pupils were equal and reacted normally to light. The carotid arterial pulsation was accentuated. In the second intercostal space of the right anterior chest there was a pulsation in the midclavicular line over which a systolic thrill was palpable. The heart was found to be enlarged. The rhythm was regular at a rate of 80. Systolic and early diastolic murmurs were heard at the apex, increasing in intensity at the sternum and over the aortic area. Harsh systolic and blowing diastolic murmurs were audible over the thoracic pulsation. The blood pressure was 170 mm. of mercury systolic and 40 mm. diastolic in each arm. The lungs were clear to auscultation. A roentgenogram of the chest is shown in figure 2A. Her blood was found to give a strongly positive test for syphilis; the cerebrospinal fluid Wassermann test was negative.

Therapy was begun with potassium iodide daily and bismuth subsalicylate each week. In the course of the next three years she received 83 injections of bismuth, 15 injections of neoarsphenamine, and 10 injections of mercury oxinamide.

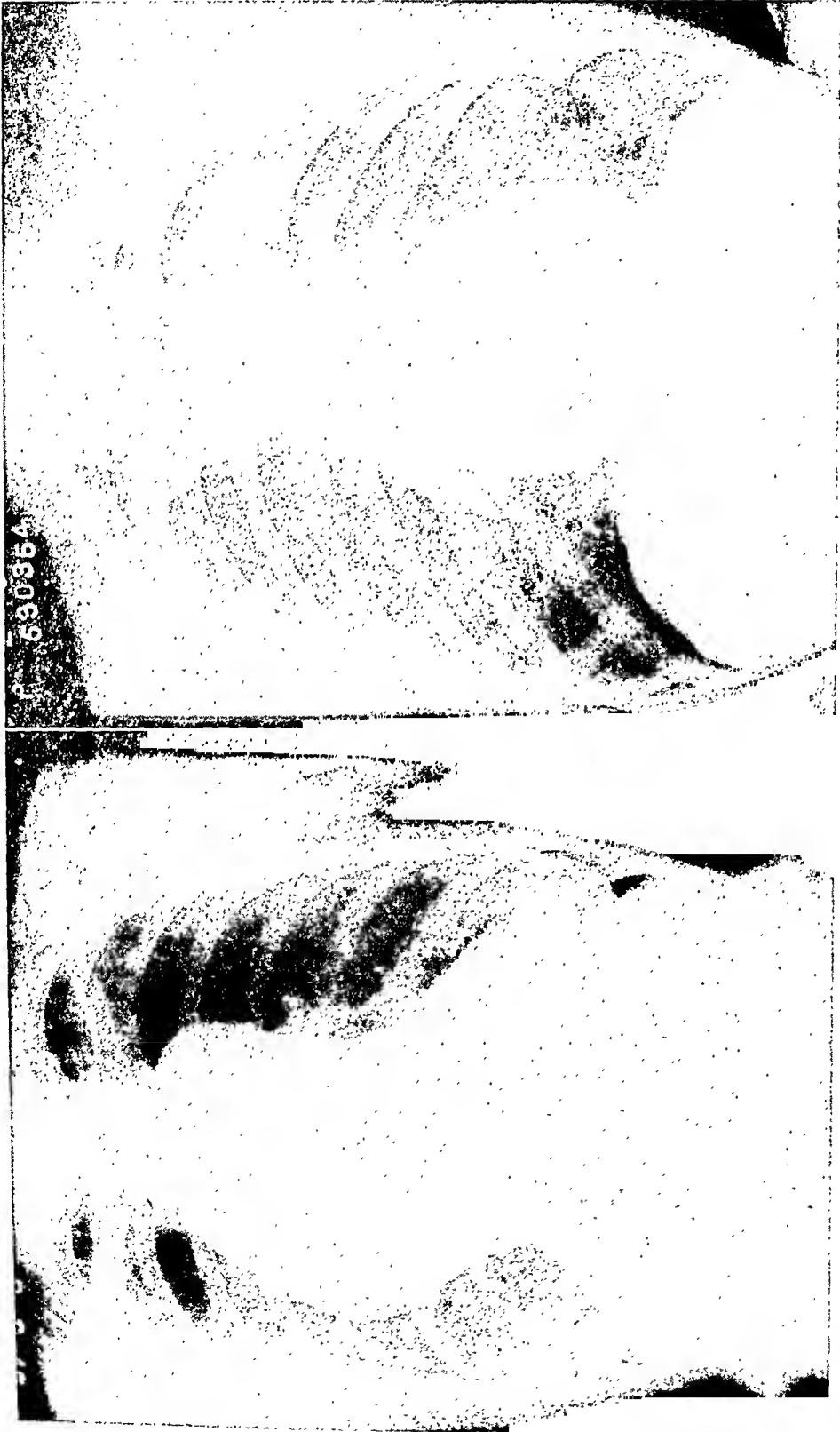
The patient did remarkably well and experienced no further dyspnea or angina. About one year after the institution of syphilitic treatment her cough disappeared. The electrocardiograms in 1941 and 1946 were normal.

In 1941 a pelvic operation was performed which was withstood well by the patient, but later there developed considerable swelling of the ankles and the joints of the hands. This subsided in a few months. Her most recent physical examination, in December 1946, showed no appreciable change from that of August 1938. A chest film showed very little change in the appearance of the aorta. She continued to feel well and denied having dyspnea or orthopnea. She was able to climb two flights of stairs several times a day without significant difficulty. The patient insists that during the past year the right anterior chest pulsation has been less.

Cough was the presenting complaint of this patient, as is not infrequently the case in patients with aneurysms of the aorta where it is attributable to pressure upon the trachea or one of the bronchi. The subsidence of cough and the apparent decrease in size of the aortic aneurysm during and following therapy certainly would suggest scar formation in and about the aneurysm. No definite heart failure was evident, but there was a history suggestive of paroxysmal nocturnal dyspnea before treatment. This patient's duration of life after the onset of symptoms is unusual.

*Case 6.* A 58 year old colored porter was first seen in the hospital in May 1946. For six months he had noted a full sensation in the throat associated at times with difficulty in breathing and a dry, hacking cough. He had had a chancre at the age of 25 which had disappeared spontaneously in three weeks; he had had no subsequent therapy.

Physical examination at this time revealed a rather thin, colored male in no great distress. The eyes were not remarkable. There was rather striking distention of the left cervical vein. The trachea was deviated markedly to the right, and there was a definite tracheal tug. Blood pressure in each arm measured 160 mm. of mercury systolic and 100 mm. diastolic. The aortic second sound was accentuated and "tambour" in quality. No diastolic murmur was heard. The heart was not thought to be enlarged. The abdomen and extremities were normal. A roentgenogram of the chest is demonstrated in figure 2B. The electrocardiogram was found to be within



A

B

FIG. 2.

*A. Case 15.* The aneurysmal dilatation of the ascending aorta with extension into the right chest is evident. The trachea was found to be displaced anteriorly and to the right.

*B. Case 6.* Multiple sacular aneurysms are evident, involving the arch of the aorta with striking displacement of the trachea to the right. The aneurysm extending to the right was found to be completely scarred and contained no blood.

normal limits. Laryngoscopic examination revealed paralysis of the left vocal cord indicating left recurrent laryngeal nerve palsy.

The patient's cough continued and was definitely brassy in character. He also noticed considerable difficulty at times in breathing associated with a wheezing in his chest. In February 1947 he was admitted to the hospital for the purpose of wiring or wrapping with cellophane one or more aneurysms of the aorta. The first operation revealed a thrombosed aneurysm of the innominate artery. The trachea was intimately attached to it and was adherent over the anterior surface of the aneurysm. A dissection of the trachea away from the aneurysm was attempted but could not be accomplished without tearing one of the two structures.

The patient continued to have considerable cough and periodic difficulty in breathing. On July 26, 1947 he was readmitted to the hospital again because of increasing difficulty in breathing, and he died within four days from tracheal obstruction.

This patient died primarily of tracheal obstruction resulting from pressure of an aneurysm on the trachea. Cough, brassy in character, was a prominent symptom throughout his illness.

### PERICARDIAL DISEASE

*Case 7.* A 68 year old female entered the Out-Patient Department of the Massachusetts General Hospital with the chief complaint of a non-productive cough of one month's duration. For two or three months there had been a mild degree of dyspnea on climbing two flights of stairs. The patient was examined briefly at this time, and the heart was thought to be normal except for an irregular pulse at a rate of 90. No murmurs were heard, and the sounds were of good quality. The blood pressure was 130 mm. of mercury systolic and 80 mm. diastolic. The lungs themselves were clear to percussion and auscultation. A roentgen-ray film of the chest showed extensive calcification in the pericardium and some enlargement of the heart silhouette. Because of the cardiac enlargement and irregular pulse the patient was given digitalis. She was seen two months later and reported that she had been free of cough for at least six weeks. An electrocardiogram taken at this time revealed auricular fibrillation with a ventricular rate of 65. There was some depression of the S-T segment in Leads I and II. The T-waves were inverted in Leads I and  $CF_4$ , diphasic in  $CF_4$ , and positive in Leads III and  $CF_2$ . The patient was again seen six months after her original entry, during which time she had been taking digitalis; her apical pulse rate was 68. A third sound was described at the apex of the heart. A venous pressure test done at this time revealed a pressure of 13 cm. of water. There was no evidence of congestion or edema, and she was feeling well. No mention was made as to whether her dyspnea had improved; in any event, it had never been a bothersome symptom.

It seemed quite evident that a poorly controlled heart rate in auricular fibrillation was the chief cause of this patient's cough upon her original entry to the hospital. With adequate digitalization the cough promptly subsided. Although the venous pressure remained slightly elevated as a result of some constriction of the pericardium, the patient was free of symptoms.

*Case 8.* A 21 year old clerk was first seen in September 1944, having been referred with a diagnosis of calcified constrictive pericarditis. In March 1943, during a routine army examination, evidence of calcium surrounding the heart had been found and the patient was rejected. His past history was not remarkable, and he had no symptoms referable to his heart.

Physical examination at this time demonstrated a well developed and well nourished male with a cervical venous pulsation. The heart sounds were of good quality and no murmurs were heard. The rhythm was regular at a rate of 80. The blood pressure was 102 mm. of mercury systolic and 80 mm. diastolic. A slight paradoxical pulse was present. The venous pressure was found to be 11.4 cm. of water. Blood studies were normal, including the sedimentation rate. The tuberculin test in 1 to 100,000 was 1 plus.

A roentgenogram of the chest demonstrated what appeared to be calcium extending anteriorly and posteriorly over the left portion of the heart. The pulsation over this portion of the heart was meager. The transverse diameter of the heart shadow measured 13.1 cm. An electrocardiogram showed inverted T-waves in all leads (figure 1B).

On October 6, 1944, a pericardial resection was performed, following which he did fairly well, although the venous pressure remained elevated. He continued to do sedentary work, but in January 1946 he noted the onset of dyspnea, followed by some swelling of the abdomen. In April 1946 he was awakened one morning by a severe paroxysm of coughing with subsequent shortness of breath. He was admitted to his local hospital where during the ensuing week he coughed a good deal in severe paroxysms. He noticed thereafter that his legs had begun to swell, and he was placed on a low-sodium diet. The shortness of breath continued, and in June 1946 he was readmitted to the Massachusetts General Hospital, two years after the original operation.

Examination at this time demonstrated a high degree of cervical venous distention, and there was evidence of fluid in the right chest. The heart sounds had not changed appreciably, except that the pulmonary second sound seemed to be louder. Auricular fibrillation was demonstrated, with a ventricular rate of 75. The liver was found to be enlarged four fingers' breadth below the right costal border, and there was some sacral edema. The venous pressure measured 26.5 cm. of water.

A second pericardial resection was done from the right anterior approach on October 25, 1946, following which the venous pressure fell to 20 cm. of water. The patient continued to do poorly, however, and to have much cough and shortness of breath. The venous pressure rose again, to about 30 cm. of water, and he required not only the digitalis which he had been taking for many months but also periodic mercurial diuresis, after which he had less cough. The electrocardiogram of December 1946 is demonstrated in figure 1B.

Careful studies, which are being reported in detail elsewhere,<sup>13</sup> indicated probable constriction of the posterior wall of the heart and, therefore, a third pericardial resection was carried out by transthoracic approach in January 1947. After a stormy early convalescence the patient did well and he has continued in much improved health since, essentially symptom-free.

Cough was a significant and important symptom at the onset of this patient's severe heart failure and probably coincided with the onset of auricular fibrillation in April 1946. This, of course, was attributable to the obstruction of the flow of blood into the left ventricle and resulted in pulmonary congestion and right-sided failure. In retrospect the cough was an important symptom to suggest constriction of the left side of the heart.

#### CONGENITAL CARDIOVASCULAR DISEASE

*Case 9.* A 13 months' old boy was admitted to the hospital in October 1942, with the complaints of cough for one week and fever for two days. He had had a normal

full-term delivery without incident and had been well. However, his parents had noted a rattling audible respiration, which was usually worse when he had a cold.

Physical examination at this time demonstrated a loose, croupy cough but no evidence of respiratory embarrassment. The lungs were found to be normal except for a few scattered musical râles throughout the chest. The temperature on admission was 103° F., which fell to normal in two days. The cough decreased and the lungs were found to be clear on the fourth day. The leukocyte count was 12,700 on entry. He was discharged with a diagnosis of acute bronchitis.

During the subsequent four and one-half years the patient had a total of nine admissions because of cough, fever, and evidence of infection in the lungs. He continued to have a cough with rather stridulous respirations at times. He was seen in the Allergy Clinic, where only the finding of a positive skin test to egg white was reported, and repeated roentgen-ray films of the chest were interpreted as not remarkable. The cardiac silhouette was found to be normal. One observer had considered the diagnosis of congenital laryngeal stridor. The patient seemed to have grown less than was normal for his age. His tenth admission was in February 1947.

His physical examination at the age of six was unchanged. He had coarse râles both anteriorly and posteriorly. The heart was normal to examination. The blood pressure was 120 mm. of mercury systolic and 65 mm. diastolic. An electrocardiogram was found to be perfectly normal, and a roentgenogram of the chest was likewise normal. Because the presence of a right-sided aorta with a vascular ring surrounding the trachea and esophagus was considered at this time, a careful barium swallow roentgen-ray examination was made (figure 3).



FIG. 3. The roentgen-ray films of Case 9, illustrating the pressure upon the right posterior side of the esophagus in A and upon the trachea in B by the persistent right aortic arch.

The boy underwent operation in April 1947, when a vascular ring surrounding the esophagus and trachea was found with a persistent right aortic arch. The ring was severed by cutting a slightly patent ductus arteriosus and a small portion of the artery connecting the left innominate artery with the small persistent left aortic arch. This allowed a release of the pressure upon the trachea and esophagus. Following the operation the patient has been very well and has had no cough or recurrent respiratory infection.

The presence of a vascular ring in this case had resulted in pressure upon the esophagus and trachea, producing bronchitis and the symptom of cough. The possibility of a vascular ring should always be considered in infants or children who have repeated cough and respiratory infections.

*Case 10.\** A 26 year old housewife entered the hospital on June 30, 1947, complaining of progressive weakness and fatigue over a period of six months. There had been no past history of rheumatic fever, but in 1941 she had been told that she had a heart murmur. Fifteen months before entry she had noted easy fatigue and beginning weight loss which amounted on admission to 15 pounds. Six months before entry night sweats had begun, together with chilly sensations, and a basal metabolic rate was reported as plus 33. Three months before entry she had been seen in a clinic where a diagnosis of rheumatic heart disease with probable active rheumatic fever was made. Nine weeks prior to admission the patient rather suddenly developed a hacking cough which at times was productive of blood-tinged sputum. Shortly thereafter symptoms of pleurisy appeared in the right lower part of the chest and she had considerable difficulty with breathing. She was treated for pneumonia at this time with penicillin, and in the next three days she had three more attacks of pleuritic pain with exacerbation of the cough and fever. Penicillin was continued because of the recurrent symptoms for a period of 12 days, a total of 240,000 units per day.

Physical examination revealed a fairly well developed female who appeared to be quite well. The lungs were normal to examination and the heart was of normal size. A Grade 4 systolic murmur was heard over the lower sternum and to either side of the sternum, widely transmitted anteriorly. No diastolic murmur was heard, and the pulmonary second sound was not accentuated. The blood pressure was 122 mm. of mercury systolic and 78 mm. diastolic. The abdominal examination was normal, and no splenomegaly was demonstrable.

Laboratory studies showed a hemoglobin of 12 grams per cent, a leukocyte count of 6600, and a normal differential count. The electrocardiogram is reproduced in figure 1C. The urine was normal, and the sedimentation rate, which was 20 mm. per hour on entry, had fallen to 4 mm. A chest film revealed a normal cardiac silhouette. The lung fields were thought to be normal except for the possibility of some bronchiectasis at the left lower lobe. The basal metabolic rate was plus 1.

While in the hospital the patient put on three pounds in weight and seemed to gain strength during her two weeks' stay. She was discharged with a diagnosis of congenital heart disease with a patent interventricular septal defect and probable recent subacute bacterial endocarditis.

Cough was not the first symptom the patient noted, but it was a very prominent symptom at the onset of her acute illness some nine weeks before being seen by us and was undoubtedly caused by recurrent pulmonary embolism with pulmonary infarction secondary to subacute bacterial endocarditis. Patients with infection superimposed upon a patency of the ductus arteriosus may produce a similar picture.

\* Patient of Dr. Edward F. Bland, Massachusetts General Hospital.



## MISCELLANEOUS

*Case 11.* A 51 year old bank clerk was first seen in April 1947 because of paroxysmal nonproductive coughing, particularly at night, with inability to sleep for a period of four weeks. The patient attributed the cough to a recent upper respiratory infection. Three weeks before entry he had consulted his local doctor, who told him he had a heart condition and said that he should rest in bed. He was given one tablet of quinidine three times a day and after five days felt much improved; during this time the cough had subsided. He then felt quite well again and returned to work, but during the first day at work, on becoming emotionally upset, he found that the cough returned and was more severe, and he noted that at times it was accompanied by wheezing. The cough seemed to come in paroxysms, particularly at night, and was more bothersome than the shortness of breath, both of which were precipitated by any exertion.

Physical examination revealed a man who was moderately short of breath and who had frequent paroxysms of severe coughing. He seemed to move quickly, but he had neither tremor of the hand nor any eye signs to suggest thyrotoxicosis. The cervical veins were distended and there was a venous pulse present. A few moist râles were heard at each lung base, but no sibilant rhonchi were heard. The heart was slightly enlarged, and the heart action was totally irregular at a rate of about 180. No murmurs were heard. The pulmonary second sound was accentuated. The blood pressure was 130 mm. of mercury systolic and 86 mm. diastolic. The liver was enlarged, but no other abdominal organs were palpable. There was no sacral or dependent edema. Fluoroscopic examination revealed a slightly enlarged heart which measured 12.5 cm. by orthodiagraphic measurement with an internal thoracic diameter of 25.5 cm. There was a great deal of increased density throughout each lung field, somewhat more striking at the hilus. The electrocardiogram showed auricular fibrillation with a ventricular rate of 180.

The patient was digitalized with lanatoside-C and within a few hours was feeling considerably improved. That night his cough was less frequent and severe, and he was not awakened by paroxysms thereof. The following day his pulse rhythm was found to be totally irregular at a rate of 110, the pulmonary second sound was still accentuated, and there was a loud apical protodiastolic gallop rhythm. During the next week he was maintained on 0.4 mg. of digitoxin, and the apical rate varied from 92 to 120. Quinidine was given daily in increasing dosage, with a final course of 0.4 gm. every two hours for five doses. The following day the pulse was found to be regular at 80, and the apical diastolic gallop rhythm had disappeared. The patient lost 13 pounds of weight in a 10-day period. A basal metabolic rate was found to be plus 29, and the blood cholesterol was 110 mg. per cent. The blood iodine was 7.49 micrograms per cent. The patient was placed upon iodine, and two weeks later the basal metabolic rate was plus 15 and the blood cholesterol was 160 mg. per cent.

Paroxysmal auricular fibrillation resulting from mild thyrotoxicosis had produced a very fast heart rate and quite severe heart failure in this patient. The cough was the predominant symptom and was promptly dispelled by control of the ventricular rate and alleviation of the congestive heart failure.

*Case 12.* A 54 year old housewife of Turkish descent was first seen in the hospital in December 1946, with the chief complaint of a productive cough of two and one-half years' duration. At times she had raised two to three cups of frothy white phlegm per day but without hemoptysis or dyspnea. There had been considerable

fatigue. Two years before entry she had been told by her doctor that she had a heart murmur and an aneurysm of the aorta. For five months before entry she had been given morphine for the cough; this had not dispelled the cough but did result in constipation. The patient's husband was known to have had syphilis and had died of heart trouble nine years previously. She had received 35 injections of bismuth and 10 injections of mapharsen during the preceding 18 months.

Physical examination revealed inspiratory and expiratory musical rhonchi throughout the chest following an episode of coughing. The heart was found to be slightly enlarged, and there was a Grade 2 aortic systolic murmur followed by a Grade 3 aortic diastolic blow well heard along the left sternal border and at the apex. No gallop rhythm was heard. The blood pressure was 190 mm. of mercury systolic, 90 mm. diastolic. The blood serological reaction was positive for syphilis. A chest roentgen-ray film demonstrated prominence of the heart in the region of the left ventricle with considerable calcification in the ascending portion and some irregularity and widening particularly in this portion.

The patient was treated in the hospital with 4.8 million units of penicillin intramuscularly (without any Herxheimer reaction) since it was thought that her syphilitic aortitis was still active. It became apparent from observation of the patient, however, that the cough was present usually when the patient was nervous or upon arising in the morning. The sputum collected in the hospital was primarily saliva, and after considerable observation it was thought that the sputum was not coming from the chest but was actually saliva being expectorated from the mouth. The diagnosis of aneurysm was not confirmed, although the patient did have evidence of syphilitic aortitis and syphilitic heart disease with aortic valvular insufficiency. The wheezing in this case was thought to be precipitated, or at least aggravated, by the cough and was not thought to be due to failure of the heart or congestion of the lungs. With reassurance the patient improved greatly, and her cough almost disappeared.

The symptom of cough in this patient was at first attributed to the underlying heart disease. However, it became evident upon observation that she had developed a considerable cardiac neurosis as a result of prolonged treatment and that the cough was more of a symptom of anxiety and neurosis than of her syphilitic heart disease. It is therefore important to analyze critically the symptom of cough in the nervous patient, since, like sighing, it may be a manifestation of anxiety rather than of heart disease.

## DISCUSSION

During the past 30 years sporadic reports have appeared with reference to cough as a symptom of heart disease. Blind and Picard<sup>1</sup> speak of cough associated with mitral valvular disease and Wertheimer<sup>2</sup> has mentioned the cardiac cough, oftentimes spasmodic in character, as a symptom of the failing heart. Few reports<sup>3-5</sup> in the American literature give reference to cough as a significant symptom in cardiovascular disease, although textbooks on heart disease<sup>6,7</sup> mention it as a possible symptom of left ventricular failure, mitral stenosis, or aneurysm of the aorta. The fact that the cough may be an early and predominant symptom of cardiovascular disease has not been fully appreciated.

The cough may be chronic, spasmodic, or paroxysmal, depending upon the nature of the underlying cardiovascular disorder. Congestion of the

lungs is undoubtedly the most frequent cause for the cough associated with heart disease, and the pulmonary congestion is usually due to left ventricular failure or mitral stenosis. It may be only after brief exertion that the patient notices the cough. At other times the cough is chronic and may be particularly bothersome at night. It frequently is a contributing cause of insomnia, which is not infrequently associated with congestive heart failure. The cough is often a precursor of paroxysmal dyspnea, and during the paroxysm it may be a prominent and aggravating symptom. This is particularly true of patients with a high degree of mitral stenosis who have repeated episodes of acute pulmonary edema initiated by severe coughing. These episodes are less frequent and more easily controlled after the establishment of auricular fibrillation with a slow ventricular rate.

Cough undoubtedly is deleterious to some patients with coronary heart disease, since the intrathoracic pressure may equal or exceed the arterial pressure during the act of coughing in patients whose blood pressures are normally low.<sup>8</sup> Continued coughing also requires muscular work and is fatiguing to the patient.

In acute pulmonary edema the pinkish color of the sputum, when such is present, is a manifestation of the hemorrhagic congestion of the lungs. With lesser degrees of pulmonary congestion the cough may be productive of clear mucoid sputum or it may be entirely nonproductive. The stimulus for the cough in pulmonary congestion undoubtedly arises in the parenchyma of the lung and follows the same nervous pathways which account for the dyspnea. Morphine and its derivatives are very effective in reducing or eliminating both the cough and the dyspnea by reducing the sensibility of the vital nerve centers of the brain to these stimuli.

The stimulus to cough is a frequent accompaniment of the bronchial constriction found in bronchial asthma. Some patients experience a good deal of constriction of the bronchial muscles in association with acute pulmonary congestion, and this may be an aggravating and additional factor in the production of cough.<sup>9</sup> The alleviation of the excessive bronchial constriction by means of appropriate therapy may be of considerable value in these patients who demonstrate evidence of bronchial constriction.

Certain disorders of the cardiovascular system produce cough by direct pressure upon the trachea or bronchi. Aneurysms of the aorta are a classical example of this variety. The cough in these cases is seldom productive. Its brassy character, usually associated with hoarseness, results from pressure upon the left recurrent laryngeal nerve with palsy of the left vocal cord. Pressure from either an aneurysm or a large left auricle secondary to mitral stenosis is the mechanism which produces this symptom. It should be remembered, however, that tumor in the region of the hilus of the left lung can produce the same type of brassy cough. If the left auricle is large because of mitral disease, pressure upon the bronchi, especially at the bifurcation of the trachea, with separation and increase of the angle of the bronchi, may be an additional factor in the etiology of cough associated with mitral

stenosis. Wrapping aneurysms of the aorta has recently been undertaken, and this may prove to be of definite value in certain cases.<sup>10</sup>

The direct pressure of a vascular ring resulting from a congenital right aortic arch and associated anomalies easily explains the cough in these cases. This condition is illustrated in Case 9 in this report and occurs usually in infants or children. Recurrent pulmonary infection is an added factor to account for the cough and is produced by stenosis of the trachea. Since the results of surgery are so satisfactory with these patients in whom vascular rings are present, it is important to recognize them early before irreparable damage may be done to the bronchi or lungs.<sup>11-12</sup>

Since cough, like respiration, is a voluntary as well as an involuntary act, it may be a manifestation of anxiety and nervousness in the cardiac patient, as is illustrated by Case 12 of this report. Even patients with perfectly normal hearts who may have their attention focused upon such a phenomenon as extrasystoles may develop a nervous cough. It is important, therefore, to use critical judgment in evaluating a cough in the nervous patient with or without evidence of cardiovascular disease, in an effort to determine whether the cough is a manifestation of heart disease or of anxiety.

Another cardiovascular disease which may prove to be associated with cough is pericardial effusion. The distended neck veins in patients with a large pericardial effusion help to demonstrate this disease. Other conditions should be considered as the cause for cough in the cardiac as well as in the non-cardiac patient, such as acute or chronic infections of the lungs, bronchi, or trachea, pulmonary embolism and pleurisy from the resulting infarction, tumor of the lung or mediastinum, sinus disease, ear disease, and pertussis.

### SUMMARY

The importance of cough in certain patients with cardiovascular disease is emphasized and illustrative cases are presented of several common types of heart disease in which cough was a prominent symptom. Pulmonary congestion resulting from either left ventricular failure or mitral stenosis is the most common cause of cough. Other conditions, namely, aneurysms of the aorta, congenital vascular rings, and pericardial disease, may cause cough as a prominent symptom. Pulmonary embolism with infarction, which so commonly complicates heart disease, especially when the heart fails, may cause coughing as well as dyspnea and pain; it should always be looked for in such cases. Finally, anxiety alone may at times account for cough in patients with or without heart disease.

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# PREVENTION OF RECURRENCES IN PEPTIC ULCER \*

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THE thoughtful internist has reason to be dissatisfied with the present handling of the problem of peptic ulcer. Statistically peptic ulcer occupies twentieth place in the prevalence of chronic diseases in the United States. However, it rises to fourteenth place in the number of invalids disabled, to twelfth place in the annual number of working days lost, and to tenth place in the annual number of deaths from chronic diseases in this country.<sup>1</sup> Symptomatic of this discontent is the eagerness with which both physicians and victims of this disease are willing to abandon the standard methods of medical treatment and to embark on a trial of every proposed new remedy.

## STATEMENT OF THE PROBLEM

The main reason for this attitude is a confusion between the effectiveness of treatment of the individual active ulcer and its failure to prevent recurrences. The classical medical treatment for peptic ulcer was originated by B. W. Sippy in 1912 and an analysis of his first results published three years later revealed successful healing of the ulcer in 85 per cent of cases.<sup>2</sup> The present modifications of this method as applied in the leading clinics are effective in producing prompt relief and in healing the ulcer in a relatively short time in over 90 per cent of the cases. The efficacy of the Sippy regimen has recently been proved also experimentally by showing that it protects dogs against peptic ulcers induced by parenteral injections of histamine.<sup>3</sup> The only other procedure capable of such protection is gastric resection with removal of at least three fourths of the stomach.<sup>4</sup>

Therapeutic research in peptic ulcer during the past two decades has introduced certain improvements but their importance is limited by the facts that only 15 per cent of uncomplicated cases of peptic ulcer were "intractable" on the classical Sippy regimen, and that none of the new medical remedies go beyond treatment of the current ulcer episode. A possible exception may prove to be an as yet unidentified property of "enterogastrone-concentrate" described by Greengard, Atkinson, Grossman and Ivy<sup>5</sup> which will be discussed later.

## INCIDENCE OF RECURRENCES

The magnitude of the problem presented by the tendency of patients who had one episode of peptic ulcer to have subsequent episodes can best be ap-

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preciated by a review of the recently published statistics on the incidence of ulcer recurrences.<sup>6-15</sup> From data summarized in table 1 it is seen that between 10 and 36 per cent of patients have a recurrence during the first six months following a medical "cure" whereas from 46 to 93 per cent of patients have one or more recurrences within five years. These figures and the already discussed excellent immediate results with standard medical therapy make it clear that the chief unsolved problem is the prevention of recurrences. This is true regardless of the type of medical practice whether private, clinic, ward, or industrial contract. The frequency of recurrences appears to be lower in private patients. However it is hard to say whether this is due to a greater ability or willingness on the part of this class of patients to observe prophylactic measures or to better opportunities for changing medical attendants for subsequent recurrences.

TABLE I  
Incidence of Recurrences in Peptic Ulcer

Authors	No. of Patients	Type of Patients	Period of Observation					
			6 mos.	1 year	2 years	3 years	4 years	5 years
Jordan and Kiefer, 1932	392	Private		9	19	30	39	46
Emery and Monroe, 1935	1435	Clinic		79	84			93
Eusterman and Balfour, 1936	600	Private				35		50
Crohn, 1938	—	Ward		31		59	73	
St. John and Flood, 1939	225	Ward			65			78
Holland and Logan, 1941	373	Private			65	60	69	78
Natvig, Römcke and Swaar-Seljesaeter, 1943	382	Ward				62		
Bokus, 1944		Private	10					50
Raimondi and Collen, 1946	151	Industrial Contract	36		83			
Flood, 1948	233	Ward		49	54	65	75	78

### CAUSES OF RECURRENCES

Before discussion of a program for the prevention of ulcer recurrences a better perspective for the proper emphasis on individual preventive measures can be obtained by an analysis of the known "inciting" causes of such recurrences. For this purpose the figures furnished by five recent follow-up

studies <sup>7, 15-18</sup> are summarized in table 2. These data indicate that the most important known causes of ulcer recurrences are: Physical or mental fatigue, emotional disturbances, dietary indiscretions, and infections, chiefly of the upper respiratory tract. The seasonal factor which also plays an important part in recurrences of peptic ulcer was excluded from this table because only one author (Jankelson) treated it statistically, classifying 19 per cent of recurrences among his patients under this heading. The clinical experience of every physician dealing with peptic ulcer is in agreement with this list as far as it goes. However, there is one other important cause of recurrences which does not lend itself readily to statistical evaluation, namely *inadequate medical treatment*.

TABLE II  
Inciting Causes of Peptic Ulcer Recurrences

Authors	No. of Patients	Fatigue	Emotions	Infections	Diet	Misc.
		%	%	%	%	%
Einhorn, 1930	800		7	56	9	28
Emery and Monroe, 1935	1279	42	32	21	5	
Davies and Wilson, 1937	52	21	35	25		19
Jankelson, 1938	350	24		15	30	31
Flood, 1948	233	40		10	25	25

### PROPER DIAGNOSIS

The prevention of recurrences of peptic ulcer in a broad sense should start even prior to treatment with a careful diagnosis. The diagnosis of peptic ulcer should not be made lightly because it places on the patient the burden of a fairly exacting dietary and medicinal regimen and may require a far reaching reorganization of his life. Positive roentgenologic evidence of the existence of an active ulcer should be obtained if possible in each case, preferably by a competent full time radiologist. On the other hand excessive reliance should not be placed on the roentgenologic examination alone. Old scarring of the duodenum, coarse rugae, or extrinsic pressure may produce a roentgenologic appearance suggestive of ulcer. Correlation of the roentgenologic findings with the clinical history, the psychic make-up of the patient, and the physical examination—especially the presence of a sharply circumscribed tenderness over the duodenum—is important. Above all the term "ulcers" should never be used as a cliché to satisfy an inquisitive patient with functional indigestion of undetermined origin. The latter practice is unfortunately all too common and leads to a loss of proper respect for the diagnosis of ulcer among laymen. If a patient with a real peptic ulcer has acquaintances who are alleged to suffer from so-called "ulcers" but experi-



ence only minor digestive difficulties in spite of habitual violations of rules necessary for the prevention of recurrences of a genuine ulcer, he will understandably be reluctant to submit to the necessary limitations of a proper prophylactic program.

### ADEQUATE TREATMENT

The second step in a campaign for prevention of ulcer recurrences is adequate treatment. Most features of an adequate peptic ulcer regimen are generally recognized. During the first period (usually one week) the diet is limited to a milk and cream mixture administered at frequent intervals (every hour or two hours) alternating with antacid remedies. Antispasmodic medication is always employed and a sedative is usually prescribed three times a day. During the second period (also usually one week) this schedule is continued with the addition of certain bland foods but only if complete relief from pain has been achieved during the first period. The additions consist of eggs, cottage cheese, white bread, oatmeal, cream of wheat, macaroni, potatoes, and rice at meal times. Sugar, salt, and butter are also allowed. In the author's opinion great emphasis should be placed on the regularity of food intake and antacid medication during the first two periods of treatment—"not more than five minutes before or after the hour" being the usual admonition. Beginning with the third week in the average case, cooked fruits and pureed vegetables are added and the strict punctuality of the schedule is relaxed. Thereafter gradual additions to the diet are made with less frequent administration of milk and antacid remedies until the patient is usually on a general diet with certain long range precautions three months after beginning of treatment. The antispasmodic medication is carried out for at least four months, and antacids are continued for at least six months from the beginning of treatment. Sedatives are prescribed as indicated. The mentioned periods of treatment although worked out on an empirical basis correspond well to the time of healing of peptic ulcers as determined from a roentgenologic study by Cummings, Grossman and Ivy.<sup>19</sup> These authors showed that 83 per cent of ulcers without distinction of location healed in 20 to 49 days.

The only controversial part of medical treatment for peptic ulcer is whether hospitalization for the first two or three weeks of treatment should be enforced as a routine measure. Even in this respect, a certain elasticity of usage is observed, since most physicians who usually recommend initial hospitalization for patients with uncomplicated ulcer will make exceptions to this rule, while clinicians who usually treat such patients under ambulatory conditions will insist on bed rest if complete relief from pain is not obtained during the first period of treatment. Furthermore, patients in different circumstances may react in a different manner to hospitalization. It may be the only way to relax a tense prosperous businessman by separating him from his affairs while a man barely earning a livelihood for his family

may get even more tense in the hospital worrying about the loss of income and costs of his treatment. More common use of hospital and health insurance will probably overcome this objection in the future.

### DANGERS OF INADEQUATE TREATMENT

It has been our experience at the University of California gastrointestinal clinic that when patients with uncomplicated ulcer are referred as "intractable" cases the explanation often is either lack of coöperation on the part of the patient or failure on the part of the physician to take full advantage of the standard methods of therapy. There is an unfortunate tendency among many physicians to think that the type of diet briefly described above as adequate is too strict to be practical for their patients. As a result compromises are made going all the way to the vague advice to "drink a lot of milk" and the administration of antacids only three times a day. In the first place, such compromises increase the number of patients who fail to respond to medical therapy, are consequently labeled "intractable" and are often subjected to unnecessary surgical operations. In the second place, inadequate treatment may bring about a state in which the patient loses his pain almost entirely or at least partly, while activity in the ulcer continues. Many patients with ulcer are apt to be too well satisfied with incomplete relief of pain because of the favorable contrast with their previous status especially if the physician himself appears to be satisfied with anything short of complete cessation of epigastric discomfort. Even with vigilance it may be difficult to recognize such a state of low activity in patients under treatment. The disappearance of tenderness over the duodenum and of occult blood from the stools is not conclusive. Frequent roentgenologic checks are helpful, but not altogether decisive especially when the duodenum is markedly deformed. Unfortunately, they are also expensive. Probably the most reliable indication of low grade activity in ulcers under treatment is a return of pain during the later stages of the ulcer regime, or soon after cessation of treatment in the absence of known causes of recurrences. Such recurrences are often classified as "spontaneous."

### LOW SENSITIVITY TO PAIN

A group particularly difficult to handle in this respect is composed of patients who are to a marked degree hyposensitive to pain. Crohn<sup>20</sup> has shown that the proportion of such individuals among patients with peptic ulcer is almost three times greater than in the general population and that this characteristic applies to one-third of patients suffering from this disease. He also demonstrated that only a small proportion of patients with serious complications of peptic ulcer are normally sensitive to pain. Crohn's figures for pain insensitive patients with complications are: 41 per cent in those with hemorrhage, 61 per cent in those with perforation, and 73 per cent in the group with stenosis. Some patients who are markedly insensitive to

pain may have an active but entirely silent ulcer which remains unsuspected until the onset of one of the major complications draws attention to it. Other patients experience only slight to moderate epigastric distress which even if recognized for what it is disappears with inadequate treatment while the ulcer remains active and may lead to one of the serious complications.

These considerations are confirmed by the observation that not infrequently, complications of peptic ulcer occur without preceding abdominal pain. In a recent paper Radloff<sup>21</sup> found that 10 per cent of patients with complications of ulcer who were seen in an Army General Hospital among 543 cases of this disease had had no previous ulcer distress. For this reason patients with low sensitivity to pain deserve a specially strict and prolonged course of ulcer therapy with frequent examinations of the stools for occult blood and periodic roentgenological checks.

### PREVENTIVE MEASURES

*Specific Measures (Enterogastrone).* There are no proved specific preventive measures for peptic ulcer in the medical armamentarium. However, there appears to be an as yet unidentified protective property in "enterogastrone-concentrate" as prepared by Greengard, Atkinson, Grossman and Ivy<sup>6</sup> which has hopeful possibilities and which has reached the stage of trial in human beings. The status of the use of this substance in experimental animals is that it will delay or prevent the occurrence of gastrojejunal ulcer in approximately 75 per cent of dogs in which the Mann-Williamson operation has been performed. In these dogs it was reported that the gastric secretory pattern after an alcoholic test meal reverts to the normal type but it is not known whether this is a result or a cause of the protection. On the other hand enterogastrone fails to protect dogs against peptic ulcers induced by parenteral administration of histamine.<sup>22</sup>

Preliminary results with clinical use of enterogastrone in 58 patients suffering from active peptic ulcer show healing of the lesion, although in this respect it is not claimed to be more effective than the standard Sippy regimen. What is more important, in a small group of 15 patients in whom the administration of enterogastrone had been stopped there was not a single recurrence of ulcer during a period of observation ranging from 12 to 28 months and averaging 21 months. From the data in table 1 it is seen that a considerable number of patients in this group would be expected to have had recurrences during the period of observation without treatment. In the discussed series enterogastrone was injected intramuscularly in most cases for a year either three or six times a week. In other series of cases the effectiveness of oral administration of enterogastrone is being studied since experience with the prevention of ulcer in dogs showed that the protection factor is resistant to peptic digestion. The beneficial effects of enterogastrone are ascribed by its originators not to a lowering of gastric acidity but to a building up of mucosal resistance to ulceration. The results

of more prolonged observations on a larger number of patients are awaited with great interest and the American Gastro-Enterological Association has already appointed a committee to correlate the study of the effects of entero-gastrone in different institutions.

*General Measures.* The campaign for the prevention of recurrences should start while the patient is still under active treatment. In the absence of proved specific measures it consists of the education of the patient in the true nature and probable future course of his disease if proper precautions are not taken and of his "indoctrination" in preventive measures based on the known "inciting" causes of peptic ulcer (table 2).

(1) *Education.* The patient should be informed in a language understandable to him that the actual cause of peptic ulcer is unknown but that its occurrence is known to be due to a constitutional predisposition in conjunction with certain unfavorable environmental factors. Therefore while the current ulcer can be healed in a large majority of patients by medical means the tendency to formation of more ulcers will remain and should be taken care of by proper preventive measures. In the opinion of the writer it is also advisable to point out briefly to the patient the common complications of peptic ulcer. If he is not familiar with them already he is almost certain to find out about them after being informed of his diagnosis, and may do so in a distorted and alarming manner. While such a discussion serves as a warning against carelessness both during and after treatment it also offers the opportunity of reassuring an anxious patient that the complications of ulcer practically never happen on an adequate regime. The fear most frequently expressed by patients is that their ulcer "may turn into a cancer." Since the large majority of peptic ulcers are duodenal, one can fortunately be very emphatic in denying this possibility in such cases. On the other hand the physician should explain to patients with gastric ulcer that repeated roentgenologic examinations will be necessary in order to rule out the threat of cancer. If this is not done patients who have been relieved of their distress may fail to coöperate or may become alarmed that their treatment is not progressing satisfactorily. Finally the patient should be informed regarding the significance of an insidious onset of vomiting and instructed to watch his stools for the appearance of digested blood. If the patient is to receive medication containing salts of bismuth the expected discoloration of stools from this source should be explained to him at the same time.

(2) *Occupational Problems.* Physical and mental fatigue has been shown to be one of the most common causes of recurrence of peptic ulcer. In addition Lion,<sup>23</sup> analyzing the sources of emotional tension in patients with peptic ulcer, found that the majority are associated with occupational predicaments. For these reasons the physician should inform himself in detail about the nature of the patient's work, his ambitions, working hours and surroundings, how his evenings and weekends are spent, whether the patient takes regular vacations, of what duration they are and what he does

with them. In the light of this information the patient's work predicament, if any, is discussed and its importance pointed out. In addition the physician profiting from his detached point of view can often make constructive suggestions on ways to lighten the occupational load and to provide proper periods of recuperation. In the case of housewives with outside jobs this often consists of encouraging resistance to unreasonable demands by members of the family. In extreme cases a change of occupation may have to be advised. When this necessity arises it is usually in connection with occupations involving the necessity of meeting a frequent deadline such as work in a newspaper office or in a firm of income tax accountants.

(3) *Psychosomatic Relations.* The typical ulcer patient is a tense, ambitious, meticulous, overconscientious person who minimizes his pain in contrast to the usual psychoneurotic or hypochondriac patient who habitually exaggerates his symptoms because he seeks refuge in his disability. This difference in personalities has been very aptly described by Jones<sup>24</sup> and by Radloff<sup>21</sup> and corresponds well to the experience of most internists. In dealing with patients of this type and especially in trying to convince them of the necessity of observing certain precautionary measures for a period of many years, if not for a lifetime, it is necessary to take into account their personality. For instance it is often observed that patients with peptic ulcer neglect their treatment because they think that it interferes with their work. By educating them to understand the essentials of the ulcer problem it is in most instances possible not only to overcome this attitude but to change it into a meticulous observance both of the immediate therapeutic regimen and of the long range program of prophylactic measures.

Psychosomatic factors other than different kinds of work predicament also play at times an important part not only in initiating the formation of a peptic ulcer but also in bringing about recurrences. For example Feldman<sup>25</sup> recently showed in a statistical study of 1154 cases of duodenal ulcer that there was a significant increase in recurrences during the five war years (1941-46) as compared to the preceding five year period. For this reason the physician should gradually explore the family relations, financial affairs, and any other matters which may be close to the patient's heart for possible sources of emotional disturbances. In the writer's experience it is not difficult to gain the confidence of most patients who conform to the ulcer type of personality if a sympathetic attitude is shown and matters are not rushed during the first visit. If emotional problems are discovered an effort should be made to point a way to their solution or when this is impossible an attempt should be made to inculcate the patient with a more detached attitude toward his difficulties. In major cases it is necessary to enlist the services of a trained psychiatrist. However, such a necessity will arise only infrequently if the physician takes the time during each visit to learn something more about the patient's personal problems and background and to make constructive suggestions based on this knowledge.

(4) *Diet.* The physician should impress every patient with the importance of moderation in eating (especially meats), of omitting chemically irritating, coarse, or excessively hot or cold foods, of chewing the food thoroughly, and of adhering to a regular meal schedule—all for a period of many years. Such instructions to the patients should be specific in each case. Generalities are apt to leave the conscientious patient in a quandary, often influencing him to observe unnecessarily strict and possibly detrimental dietary restrictions. For the less conscientious patient they are an invitation to evade necessary limitations. The details and strictness of dietary precautions depend on the judgment of the physician. Into this judgment prominently enter the amount of scarring in the duodenum, the degree of residual hyperacidity and hypermotility, the ease or difficulty with which treatment controlled the pain, the amount of unavoidable fatigue or emotional strain, and last but not least, an estimate of the patient's tendency to discount medical advice. Any physician who has observed at social gatherings the dietary behavior of patients under his treatment for gastrointestinal ailments will know what the writer means by this statement. Accordingly in instructing patients regarding dietary precautions it may be sufficient to warn some of them not to indulge in certain foods to excess while others must be told "never" to eat these foods in order to achieve the same purpose.

(5) "*Stimulants.*" Under this heading are loosely grouped together a number of habits which patients with peptic ulcer are apt to acquire to an immoderate degree in an effort to overcome their tension or to counteract their fatigue. Many patients come to rely on coffee for this purpose. Coffee has been shown by Roth, Ivy and Atkinson<sup>26</sup> not only to heighten the acidity of the stomach contents directly but also to sensitize the gastric secretory mechanism to other secretory stimulants after the direct effect of coffee has worn off. For this reason as well as because of the general stimulating effect of coffee which enables a patient with peptic ulcer to overexert himself even more than he is already inclined to, coffee and all caffeine containing beverages should preferably be renounced by the patient. The same applies to brands of coffee from which most of the caffeine has been extracted because they still produce hypersecretion of gastric juice.

Some patients resort to alcohol for relief of their tension. Since alcoholic beverages are known to stimulate secretion of gastric juice they are contraindicated for patients who had a peptic ulcer, especially on an empty stomach and in direct proportion to their alcoholic content. The plea is sometimes made that the beneficial relaxing action of alcohol may outweigh its harmful effect on gastric acidity. The obvious answer to this is that relaxation can be accomplished more safely by administration of sedatives.

Smoking also comes under this general heading.\* Experience shows that the habit of smoking has a much firmer grip on most patients than the

\* Whether the harmful effects of smoking are due to an increase in acidity as found by Ehrenfeld and Sturtevant<sup>27</sup> or to other factors as claimed by Schnedorf and Ivy<sup>28</sup> is not finally established.

indulgence in coffee or in alcoholic beverages excepting a few hopeless alcoholics. In confirmed smokers the restlessness and distress which accompany cessation of smoking may actually overbalance the advantages to be gained by abstinence. For this reason it is usually advisable to find out from the patient how dependent he is on smoking and what his experience with previous attempts to stop smoking has been. Depending on this information it may be judged desirable in some cases to postpone an attempt at breaking this habit until the patient is over his acute ulcer attack. In the meantime a drastic reduction of smoking should be urged on the patient with the admonition to smoke only with food in his stomach. The writer finds himself forced to compromise with smoking more often than with all other habits detrimental to ulcer patients combined, with the possible exception of the urge to overwork.

Finally attempts to combat fatigue by the use of benzedrine and its derivatives as well as preparations of the thyroid hormone should be prohibited except for thyroid medication in cases of demonstrated hypothyroidism. The answer to the problem of fatigue in patients with the peptic ulcer diathesis as pointed out under "Occupational Problems" lies in the scaling down of responsibilities and working time rather than in artificial stimulation.

(6) *Infections.* Various infections, especially those of the upper respiratory tract, are notorious in initiating recurrences of peptic ulcer and probably account to a large extent for the commonly recognized "seasonal" trend of recurrences in the fall and spring months. To counteract this influence of colds the patient should be impressed with the importance of guarding against them by avoiding exposure to cold and wetness and by staying away from crowds during epidemics of upper respiratory infections. Prophylactic vaccination against influenza should be tried. Furthermore, the patient should be instructed to care properly for his colds by taking his temperature and going to bed for the duration of the febrile period, if any. Here again the typical ulcer patient is particularly vulnerable due to his great reluctance to stay home from work. Finally patients must be warned against excessive medication with antipyretics, especially aspirin, and against the use of alcohol or "cold tablets" containing caffeine in the treatment of colds. Chronic focal infection, especially of the teeth and nasopharynx, should be looked for and eradicated if found.

(7) *Seasonal Factors.* The occurrence of new peptic ulcers, of recurrences, and of complications of ulcer predominantly in the fall and spring of the year is well recognized. As already pointed out, the prevalence of upper respiratory infections during these seasons probably plays an important part in this distribution of morbidity. Further evidence in favor of this explanation is the "mono-seasonal" intensification of ulcer activity which has been observed in parts of the country with a mild climate where fall is the chief season for colds. Aside from efforts to control colds no specific precautions can be recommended against the seasonal factor except for special

vigilance in regard to other causes of recurrences at these times. In extreme cases with a history of unexplained recurrences during the fall or spring routine institution of a protective regime to be discussed below is advisable during these seasons.

(8) *The Human Equation*. In discussing the handling of peptic ulcer, Palmer<sup>29</sup> wrote: "The results depend on the patient—his willingness and ability to coöperate, and on the physician—his knowledge, personality, tact, enthusiasm, persistence, resourcefulness and painstaking care. . . ." The daily observance of precautions for many years is a tedious affair, especially since the objective—the absence of recurrences—is a *negative* reward. In properly handling patients with peptic ulcer the physician will often need all of the mentioned qualities and, in addition, must maintain an active interest in the preventive program in order to keep up the patient's interest. In outlining a long range program for prevention of recurrences the physician should allow the patient every leeway justifiable in the individual case lest by insisting on excessively strict measures, from the patient's point of view, the latter be prejudiced against the whole preventive program.

A balance in this respect can be struck by asking the patient to observe only a minimum of routine restrictions after the first year marked by an absence of recurrences. In return, the patient should return to a fairly strict protective regime during periods when the known causes of recurrence are unavoidably present, with emphasis on the factors which have brought on past recurrences in the particular patient. Such a protective regime consists of a bland diet with a glass of milk between meals, antacid medication and antispasmodic as well as sedative preparations. At the same time the patient should increase his periods of rest at the expense of unessential activities and if possible also reduce his working load. Patients with low pain sensitivity should be especially careful to resort to the protective regime when exposed to conditions favoring recurrences.

When explaining to the patient with peptic ulcer the nature of his disease and talking over measures for the prevention of recurrences it is a good practice to invite on one or two occasions the patient's spouse in order to secure marital supervision of the patient's performance. If the number of patients under treatment for peptic ulcer warrants it, classroom instructions as introduced in Boston by C. M. Jones may be carried out. In addition to verbal instructions it is wise to supply patients with a printed list of precautions which they are asked to read over once a month. Another way of increasing the patient's comprehension of the ulcer problem and of assisting his memory in observing precautions is to advise him to buy and read a popular booklet on peptic ulcer published by Harper and Bros.<sup>30</sup>

(9) *Prompt Treatment of Recurrent Epigastric Distress*. In addition to following the described precautionary measures, each patient should be prepared to handle any recurrence of suggestive ulcer pain by going promptly on the first stage of the strict ulcer diet and reporting at once to his physician. For this purpose and also for the institution of the protective regime



as previously discussed, it is advisable for patients to keep a supply of the antacid and antispasmodic medications at home. In case of rapid disappearance of epigastric distress after beginning of therapy an abbreviated course of treatment is permissible at the discretion of the physician. This is especially true if there is no occult blood in the stools and if radiological evidence of active ulceration is missing. Many recurrences of pain, particularly in duodenal ulcers, are initially due to irritability and spasm, but if neglected will result in a full fledged ulcer. In a properly instructed and coöperative group of patients under medical supervision it should be possible to prevent a large percentage of episodes of recurrent epigastric distress from developing into real ulcers. In this way the striking figures for invalidism, loss of working time, and deaths from peptic ulcer quoted at the beginning of this paper could be materially reduced.

### SURGICAL MEASURES

In discussing the prevention of recurrences of peptic ulcer it is necessary to point out the place occupied by surgical operations which have a preventive effect. Since the use of gastro-enterostomy has been limited in the leading clinics to a few selected cases because of the high (up to 40 per cent) <sup>31</sup> incidence of gastro-jejunal ulcers following in its wake, there are at present only two operations which merit serious considerations.

*Subtotal gastrectomy* when properly performed results in marked diminution of gastric acidity by removal of most of the acid secreting part of the stomach, by neutralization of gastric contents with intestinal juice, and by increasing the rate of gastric emptying. Experimentally this operation protects dogs from peptic ulcer induced either by the Mann-Williamson operation or by parenteral injections of histamine, provided that 75 per cent of the stomach has been removed.<sup>4</sup> The published surgical mortality of subtotal gastrectomy is low (usually under 5 per cent) considering the magnitude of this operation. However it must be borne in mind that these reports come from some of the best hospitals in the country where highly trained surgical teams are operating on patients who had excellent preoperative preparation, anesthesia by the latest methods, and modern post-operative care. There are reasons to think that the mortality is much higher when this operation is performed by an average surgeon in an average hospital, and that below a certain level of surgical skill and technical assistance it may become prohibitive.

The end-results of subtotal gastrectomy from the point of view of recurrences are said to be good in about 90 per cent of cases, although Lahey <sup>32</sup> recently introduced a discordant note by reporting 28 recurrences of massive hemorrhage in 100 patients subjected to this operation. A considerable portion of patients experience some difficulties in their new physiological state which consist of nausea, anemia, weakness, inability to maintain normal weight, or the syndrome called "dumping stomach."

*Vagotomy*, when complete, reduces gastric acidity and motility by

abolishing the cephalic phase and weakening the reflex phase of gastric function.<sup>33</sup> Experimentally this operation retards but does not prevent histamine provoked peptic ulcers in dogs.<sup>34</sup> In man, vagotomy counteracts the harmful effects of tension in promoting excessive gastric acidity and motility. On the other hand vagotomy fails at least partly to protect against stimulating humoral influences on gastric secretion such as histamine,<sup>35</sup> caffeine, alcohol and nicotine. From these considerations it appears that vagotomy can be expected to provide less complete protection than subtotal gastrectomy and that the degree of protection depends on the cause of hypersecretion in a given individual. Technically the operation is less formidable than gastrectomy but involves a possible pitfall in incomplete section of all vagus fibers especially when performed through the abdominal approach even by an expert. The surgical mortality in the experience of the foremost surgeons is so low that it can be considered negligible. No data on mortality in the hands of "average" surgeons are available.

It is premature to speak about the "end-results" of an operation which was introduced only five years ago. During a symposium on vagotomy at the 1947 Annual Meeting of the American Surgical Association, a total of about 500 well controlled cases, only a minority of which had been followed longer than two years, were reported. In the larger of these series the therapeutic as well as the prophylactic results to date were favorable in about 90 per cent of patients. As in the case of subtotal gastrectomy several difficulties of a chronic nature may develop postoperatively, the more important of which in the gastrointestinal tract are diarrhea and gastric stasis with foul belching and vomiting. This may require subsequent reoperation for gastro-jejunostomy or subtotal gastrectomy. The transthoracic approach for vagotomy may lead to another set of complications of which the most distressing is persistent intercostal neuralgia.

In summarizing the preventive results of modern surgical operations for peptic ulcer it can be stated that when performed by experts the large majority of patients are better off than before the operation, provided that the latter was undertaken for valid indications. Such indications are true intractability of the ulcer on a strict medical regime in a hospital, frequent disabling recurrences of the ulcer in spite of an adequate prophylactic regime, and inability or unwillingness on the part of the patient to follow such a regime. These criteria should be applied very strictly to patients who are relatively insensitive to pain in order to prevent the appearance of serious complications with little or no warning. Even after a successful operation the patient should be urged to observe a medical prophylactic regime, more so after vagotomy than after subtotal gastric resection. The best that can be said of the prophylactic value of the discussed operations is that a considerable portion of patients feel entirely well after the operation without observing any precautions. The worst that can be said about them is that even among the foremost surgeons there are advocates of routinely combining vagotomy with subtotal gastrectomy or gastro-jejunostomy.

## SUMMARY

1. Dissatisfaction with the present handling of the problem of peptic ulcer should be directed not so much at the results of medical treatment of the current ulcer as at the failure to prevent recurrences.

2. Data are cited which indicate that ulcer recurrences are so frequent in all types of medical practice that with some exceptions peptic ulcer should be considered an incurable disease which must be kept under control by appropriate measures.

3. Recurrences of peptic ulcer are associated with four main "inciting" causes: Physical and mental fatigue, emotional disturbances, dietary indiscretions, and respiratory infections.

4. Prevention of ulcer recurrences should start with proper diagnosis and *adequate* medical treatment. Failure of physicians to insist on a strict and sustained regime decreases the percentage of successful cases and results in early recurrences of peptic ulcer which eventually lead to serious complications. This applies particularly to patients with low sensitivity to pain.

5. It is the duty of the physician to inform patients with peptic ulcer of the true nature and probable course of their disease and to convince them of the necessity of long continued preventive measures.

6. The preventive measures proper consist of:

- a. Elimination of overwork and adjustment of occupational predicaments.
- b. Attention to psychosomatic factors.
- c. Precautions in regard to diet and so-called "stimulants."
- d. Prophylaxis and therapy of respiratory infections.
- e. Institution of a protective regime during periods of unavoidable stress.
- f. Prompt treatment of recurrences of epigastric distress.

7. The surgical operations of subtotal gastrectomy and vagotomy are discussed from the point of view of prevention of ulcer recurrences and of indications for surgical intervention.

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# VISCERAL THROMBOPHLEBITIS MIGRANS \*

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A REVIEW of the development of the concept of peripheral thrombophlebitis migrans has been presented by Barker.<sup>1</sup> Clinical evidence of vein involvement in the viscera was described as early as 1866 by Sir James Paget.<sup>2</sup> Since then there have been additional reports of visceral migratory thrombophlebitis with recovery in most instances. The first fatal case in which a postmortem examination was performed was reported by Kramer<sup>3</sup> in 1925. Subsequently, four additional cases with autopsy were described.<sup>4, 5, 6, 7</sup> Two other cases of multiple venous thromboses with autopsy were published under the title of "Thrombophlebitis migrans."<sup>8, 9</sup> In neither case was visceral thrombophlebitis present, nor was phlebitis the cause of death.

During the past 12 years, six cases of thrombophlebitis migrans with visceral vein involvement have come to autopsy at The Mount Sinai Hospital, New York. The disease was primary in that it was not associated with known causes such as trauma, bacterial infection, neoplasm, etc. A comprehensive description of these cases will be presented and those previously reported reviewed, with a view to the establishment of visceral thrombophlebitis migrans as a clinical and pathological entity.

## CASE REPORTS

*Case 1.* The patient, a 21 year old white female, was admitted to the Medical Service of Dr. George Baehr on April 6, 1944. She was well until four weeks before admission when she developed fever, headache and malaise which subsided in three days. She remained well for two weeks following which she experienced a sharp pain in the left hip with fever to 103° F. Three days later pain appeared in both calves. One week before admission she developed right chest pain followed by nausea, vomiting and three small hemoptyses. Examination revealed an acutely ill patient with a temperature of 102.6° F. and respirations at 28 per minute. There was tenderness over the left calf and left femoral region, a positive Homan's sign on the left and a localized tender area about one and one-half inches long over the inner aspect of the right mid-thigh. Dullness to flatness, diminished fremitus, bronchovesicular breathing and crepitant râles were elicited over the right lower lobe.

A diagnosis of bilateral femoral thrombophlebitis was made. It was thought that the pulmonary manifestations were caused by emboli. In order to prevent further embolization both femoral veins were ligated and heparin was administered for two days. During this time the wound oozed and her hemoglobin fell to 42 per cent (Sahli). The leukocyte count was 21,000 per cu. mm. Following several blood transfusions her general condition improved, although fever, moderate anemia and leukocytosis persisted. Various agglutination tests (typhoid and paratyphoid, brucella, heterophile, cold and proteus × 19) were negative. A roentgen-ray ex-

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From the medical services of Dr. George Baehr and Dr. Isidore Snapper, The Mount Sinai Hospital, New York.

amination of the chest revealed a density in the right lower lobe and a fainter one in the left lower lobe. Sulfonamides did not reduce the fever. On her seventeenth day in the hospital she complained of abdominal pain. This persisted for five days and was followed by vomiting. The vomitus gave a three plus guaiac reaction. Intraperitoneal puncture yielded bloody fluid, confirming the impression that infarction of the bowel had occurred. The following day she developed diffuse abdominal rigidity, tenderness and marked distention. Despite intensive supportive therapy she died 26 days after her admission to the hospital.

*Pathological Findings.* The essential findings were as follows: The abdominal cavity contained one liter of sanguineous fluid. There was hemorrhagic infarction of the entire jejunum. The spleen was enlarged (400 gm.) and congested. The liver appeared fatty and the remainder of the abdominal viscera were congested. The portal, splenic, superior mesenteric, gastric and gastroepiploic veins were occluded by thrombi. The pleural cavities each contained about 400 c.c. of hemorrhagic fluid. There were recent and somewhat older infarcts in all lobes of the right lung and in the left lower lobe. There were partially organized emboli in various branches of the pulmonary artery. No essential gross abnormalities were found in the heart. There were partially organized thrombi in both renal veins but except for some congestion of the medulla the kidneys were not significantly altered. The veins of the adrenal glands and pancreas contained scattered thrombi. These organs, however, were not grossly changed. Parietal thrombi were present along the course of the inferior vena cava. Both common iliac and femoral veins were occluded by firm, red blood clot.

Histologic examination revealed thrombi in various stages of organization in the involved visceral and peripheral veins. An inflammatory cell infiltration of the adventitia and about the vasa vasorum was seen in the sections of the splenic and iliac veins. The inferior vena cava showed occasional inflammatory cells in the intima at a site distant from an organizing parietal thrombus. The jejunal walls were infiltrated with red cells and were necrotic. The lungs showed hemorrhagic necrosis (infarcts) in various stages of organization; the pulmonary artery branches were occluded by thrombotic masses. The remaining viscera were only congested.

*Case 2.* This 45 year old white male was admitted to the Neurologic Service of Dr. Israel Strauss on May 21, 1935. Eighteen months before he had had an episode of weakness, fatigability and difficulty in sleeping which lasted for several days. This had been followed three weeks later by visual disturbances and strabismus. He was now admitted for investigation of the strabismus. Following intensive study it was concluded that his strabismus was probably due to a lesion in the brain stem rather than to any primary ocular disturbance. At this time he was found to have chronic sinusitis and an unexplained eosinophilia of from 20 to 43 per cent. All other examinations revealed no significant abnormalities. He was given a course of anti-leptic therapy despite a negative blood and spinal Wassermann reaction. During the following two and one-half years the function of his eye muscles improved.

On January 15, 1940 he was admitted to the Medical Service of Dr. George Baehr, this time complaining of dyspnea, orthopnea and ankle edema. About two and one-half years prior to this admission a physician told him that the veins on his chest and abdomen were dilated. Six months later he noted dyspnea on exertion. Two months before this admission he noticed enlargement of the abdomen associated with some epigastric pain. Five weeks later he developed pain in both sides of the chest and slight cough productive of small amounts of non-bloody sputum. The cough gradually subsided but the dyspnea became more pronounced and was followed by ankle edema. On examination numerous dilated veins were seen over the chest anteriorly and posteriorly, and over the abdomen; a left varicocele was also present. There was weakness of both right and left eye muscles. The lungs were clear except

for diminished resonance over the right lower lobe. The heart was apparently normal. The liver was palpated four centimeters below the costal margin. Ascites and abdominal distention were present. Movements were clumsy and the sensorium somewhat sluggish. The blood pressure was 148 mm. of mercury systolic and 104 mm. diastolic. There was no dyspnea, orthopnea or edema at this time.

Inasmuch as the diagnosis was unclear the patient was subjected to a series of investigative procedures. The blood count revealed only a mild secondary anemia with no eosinophilia at this time. Urinalysis was negative. Chemical studies of the blood were within normal limits. The circulation time was 24 seconds (saccharin) and the venous pressure 27 to 30 cm. of water. A roentgenogram of the chest revealed an irregularly loculated collection of fluid over the right lung and apex, the irregular distribution being ascribed to pleural adhesions. The right leaf of the diaphragm was elevated. Roentgenkymogram revealed diminished pulsations over the mid-portion of the left ventricle and the right superior mediastinum. This was interpreted as suggestive of pericardial adhesions. Pneumoperitoneum, gastrointestinal roentgen-ray examination and other studies failed to clarify the clinical picture. The electrocardiogram was normal except for low voltage in all leads. Reëxamination by the neurologists was productive of no new conclusions.

The diagnosis of constrictive pericarditis was considered, although the possibility of multiple venous thrombosis and occlusion was also suggested. The chest fluid re-accumulated rapidly necessitating thoracentesis on five occasions. Search for tumor cells was negative. Finally, exploratory thoracotomy was performed on February 9, 1940 and a normal pericardium was found. Subcutaneous emphysema developed post-operatively and despite release of the sutures, the removal of air from the left chest and fluid from the right, the patient failed to rally and died on the night of operation without having regained consciousness.

*Pathological Findings.* The significant gross alterations were as follows: There was extensive subcutaneous emphysema of the neck and chest. The lungs were collapsed and each pleural cavity contained about 500 c.c. of hemorrhagic fluid. The pericardium had been laid open by a longitudinal surgical incision and its edges fixed to the chest wall. The pericardium was otherwise normal. The heart and lungs did not reveal any other abnormalities. The superior vena cava was converted into a solid cord beginning at a point about 3 cm. above its entry into the right auricle and extending for a distance of 8 cm., thereby including the right internal jugular vein. The most mesial portions of the right subclavian and azygos veins were likewise occluded. The remainder of the azygos vein contained several small organized thrombi. There were extensive collateral venous channels in the chest wall, diaphragm and about the esophagus. The esophageal and gastric veins were markedly distended. At the point of junction of the inferior vena cava with the hepatic veins there was a half-moon shaped, partly calcified, organized thrombus, producing marked stenosis of the vena cava. Above and below this point there were several small recent adherent thrombi. The ostia of the hepatic veins were funnel shaped and markedly stenosed. The liver was not significantly enlarged (weight 1450 grams) and only moderately congested. On cross section of the liver many of the larger hepatic veins were seen to be occluded by old thrombi. The spleen was not enlarged. There was a large amount of straw colored fluid in the abdominal cavity. The right renal vein was obliterated by old organized thrombi. The kidneys were congested. The spermatic veins were dilated and filled with dark red thrombi. The remaining organs were not abnormal.

Histologic examination revealed obliteration of the lumina of the superior vena cava, right internal jugular vein, right subclavian, azygos and right renal veins by old organized thrombi, with varying degrees of recanalization. A similar picture was seen in the larger hepatic veins. The thrombotic mass in the inferior vena cava



was partially calcified and organized. There were also fresh thrombi in the smaller hepatic veins with an occasional one showing acute necrosis of the subintimal tissues. The liver and kidneys were markedly congested. Except for moderate congestion, the remaining viscera were not significantly altered.

*Case 3.* A white male chauffeur, 42 years old, was admitted to the Medical Service of Dr. George Baehr on January 28, 1933. Eight years before admission he had pleuritis and was ill for four months. One month prior to admission he was ill with what was termed "grippe." On the day preceding hospital admission he was seized by a severe pain in the right lower chest, followed by fever, cough and tenderness. Examination revealed diminished respiratory excursion on the right with dullness, decreased fremitus and distant breath and voice sounds. The temperature was 101.6° F. and the leukocyte count 25,000 per cu. mm. with 85 per cent polynuclears of which 15 per cent were staff cells. Several days later there were signs of frank consolidation over the right lower lobe with bloody sputum. It was thought he had a right pleural effusion covering a lobar pneumonia. On the ninth day after admission he complained of pain in the left chest; at this time the signs on the right were subsiding. Fever and tachycardia persisted, however, and signs of consolidation of the left lower lobe subsequently appeared. Five days later he complained of pain in the legs followed by pitting edema of the feet and ankles and tenderness in the calves and thighs. The right leg became edematous and an erythematous area appeared in the right groin. The following week the entire right flank and buttock became edematous and the abdomen was distended. Subsequently, he developed sacral edema and a brawny induration of the right leg and foot. Physical signs of consolidation of the left lower lobe and bloody sputum were still present four weeks after admission. Thickened, thrombosed veins were palpable in both groins and thighs. Six weeks after admission he complained of pain in the arms and umbilical area. These symptoms appeared intermittently over a period of 12 days and were associated with fever and leukocytosis of 17,000 per cu. mm. Three weeks later pain, edema and tenderness of the right side of the neck developed and the right external jugular vein was found to be involved. Repeated urinalysis revealed a specific gravity range of 1.006 to 1.030 with an occasional faint trace of albumin. All his symptoms gradually subsided and he was discharged on April 23, 1933.

On October 26, 1934 he was readmitted to the hospital, not having been seen in the interim. He stated that except for dependent edema of the legs he had been quite well until six months before this admission when he had an itching eruption about the ankles with erythema and vesicles of the soles of the feet which subsided. Two months prior to re-admission there was a marked increase in leg edema with extension to the lower abdominal wall, unrelieved by bed rest. Subsequently, puffiness of the face and neck developed. On examination, there was pitting edema of the legs, thighs and presacral area. The heart and lungs were normal; the blood pressure 114 mm. of mercury systolic and 66 mm. diastolic. Urinalysis revealed four plus albumin, a few leukocytes, occasional hyaline and many granular casts. In the urine concentration test the specific gravity varied from 1.028 to 1.034. The blood chemical studies revealed hypoproteinemia (total protein 3.4 gm. per cent; albumin 1.9 gm. per cent; globulin 1.5 gm. per cent). The cholesterol was 735 mg. per cent, chlorides 595 mg. per cent, urea nitrogen 19 mg. per cent. The basal metabolic rate was minus 16. He was placed on a low salt, high protein diet with restriction of fluids. Despite this therapy, he developed ascites and increased edema of the legs and abdominal wall. Mercupurin failed to reduce the edema. He did, however, respond to oral urea therapy with occasional daily excretion of 160 ounces of fluid. During this hospital stay he developed pharyngitis and otitis media which responded to conservative therapy. At the time of discharge his blood proteins had risen to 6.2 gm. per cent, with 3.7 gm. per cent albumin and 2.5 gm. per cent globulin. The urea re-

mained low, 16 mg. per cent. A Congo red test showed 62 per cent tissue absorption. Albuminuria persisted varying from one to four plus. He left the hospital on February 5, 1935 with considerable improvement in his condition. The discharge diagnosis was subacute glomerulonephritis in the nephrotic phase.

Three months later, on May 3, 1935 he was re-admitted because of re-accumulating edema, despite a high protein diet and intensive urea therapy. On examination he appeared pale. There was pronounced edema of the skin of the entire body; the scrotal sac was filled with fluid and ascites was marked. The blood count was normal. The blood chemical studies revealed a total protein of 3.7 gm. per cent with 1.6 gm. per cent albumin and 2.1 gm. per cent globulin; the cholesterol was 590 mg. per cent and the urea nitrogen 24 mg. per cent. There was a pronounced albuminuria with numerous granular and hyaline casts. Two weeks after admission the patient developed erysipelas of the right arm and right side of the body with fever and leukocytosis of 14,800 per cu. mm. One week later a recurrence of the thrombophlebitis of the right leg was observed, with tenderness, erythema and pronounced edema. The erysipelas spread to the left side of the body and the patient died on June 1, 1935. The diagnosis at death was still subacute glomerulonephritis in the nephrotic phase.

*Pathological Findings.* The essential gross alterations were as follows: There was extreme anasarca with denudation of the skin about the hips and thighs. A considerable amount of fluid was found in the abdomen. The lungs showed scars, presumably of old infarcts, in the lower lobes. There was a recent, partially organized thrombus in the pulmonary artery branch to the right upper lobe. There were no gross changes in the corresponding pulmonary segment. The heart was normal. The superior vena cava, innominate veins and lower segments of the internal jugular veins were normal. The other veins of the head and neck could not be examined because of limited autopsy permission. The liver showed only moderate congestion; the portal and hepatic veins were normal. The spleen was enlarged and the splenic and superior mesenteric veins were the seat of an old thrombophlebitis as evidenced by the presence of filmy, recanalized tissue along the walls. The intestines were congested and edematous. The kidneys were large, pale, yellow gray and showed marked congestion, particularly of the medulla. The glomeruli seemed quite prominent. Both renal veins were completely replaced by a filmy, recanalized tissue. In addition, the left renal vein contained recent, granular, red thrombi in the recanalized channels. The left adrenal and spermatic veins presented a similar picture. The right adrenal gland was absent (congenital). The inferior vena cava, beginning at a point four centimeters below its junction with the hepatic veins, was transformed into a cavernomatous cord for its entire length. This transformation extended into the common iliac and femoral veins as far as could be traced through the abdominal section. The veins were embedded in dense scar tissue. There were no significant systemic arterial changes.

On microscopic examination of the involved veins the lumina were seen to consist of a series of newly formed channels of varying size, separated by connective tissue. There were, in addition, recent thrombi in the new venous channels in the left renal and adrenal veins. The lungs revealed areas of dense scar tissue at the site of old organized infarcts. The thrombus in the right upper lobe branch artery was the seat of partial fibroblastic organization. There was congestion of the sinuoids of the spleen and liver. There were small foci of hemorrhage and collections of round cells in the left adrenal gland. The kidneys revealed a moderate increase in interstitial connective tissue with lymphocytic infiltration. The capillaries throughout were wide and congested. The epithelium of the glomeruli and tubules were filled with doubly refractile lipid. The glomerular capillaries and intra-parenchymal vessels were unaltered. There was no evidence of glomerulonephritis.

*Case 4.* The patient, a 24 year old white female, was admitted to the Medical

Service of Dr. George Baehr on January 6, 1942 complaining of bleeding gums, menorrhagia, easy bruising and the appearance of reddish purple spots on the chest, arms and legs, all of one month's duration. Her first pregnancy, six years previously, was aborted spontaneously in the fourth month and at that time she was told that she had hypertension and kidney disease. Her second pregnancy terminated in a premature delivery at seven months. She was again told she had hypertension.

On examination numerous purpuric spots were seen over the face, neck, arms, chest and legs. The gums bled easily. Menses had not yet ceased. Aside from the presence of a soft, apical systolic murmur the remainder of the physical examination revealed nothing of significance. The blood pressure was 98 mm. of mercury systolic and 70 mm. diastolic. The tourniquet test was positive, the bleeding time 30 minutes and the clotting time 6. There was a pronounced delay in clot retraction. The hemoglobin was 45 per cent (Sahli). The erythrocyte count was 3.4 million, the leukocytes 9,600 per cu. mm. with a normal differential. Only 10,000 platelets per cu. mm. were found. Bone marrow smears revealed a cellular marrow with a normal distribution of marrow elements; the megakaryocytes were normal in number but many immature forms were seen. The spleen edge was felt after admission. Splenectomy was advised and performed on the second day of hospitalization. Following operation atelectasis of the left lower lobe developed; the pulmonary signs cleared within several days. The platelets gradually rose to 360,000 per cu. mm. and there was a post-operative leukocytosis of 23,700 per cu. mm. Routine blood chemical studies were within normal limits. The patient's condition gradually improved after operation and she was discharged on January 22, 1942 two weeks after splenectomy. The pathological report was "Spleen without significant change, compatible with clinical diagnosis of thrombocytopenic purpura. Weight 185 grams."

Three years later, on January 21, 1945, the patient was readmitted because of fever, chest pain and cough of three days' duration, preceded by a shaking chill. Since her first admission she had had a normal delivery and had otherwise been well except for the presence of a dry, scaling, erythematous eruption over the cheeks and bridge of the nose of two years' duration. Examination at this admission revealed signs of a right pleural effusion, and possibly also of a left. The blood pressure was 105 mm. of mercury systolic and 75 mm. diastolic. There was a flush over the nose and cheeks with slight scaling. The right pleural cavity was aspirated and 1500 c.c. of sero-sanguineous fluid were removed. The blood count showed persistent leukocytosis to 21,000 per cu. mm. with 84 per cent polynuclears. The erythrocyte and platelet counts were normal. A roentgenogram of the chest confirmed the presence of a bilateral pleural effusion; the heart appeared enlarged. An electrocardiogram revealed right axis deviation. The temperature, 103° F. on admission, gradually fell to normal. The right pleural cavity required aspiration on two other occasions. The patient's condition improved and she was discharged on February 15, 1945.

She was admitted for the third time on August 21, 1945 again with fever, chest pain and malaise of three days' duration. A history of recurrent colds and frequent cough was now obtained. Examination at this time revealed the presence of fluid in the left pleural cavity and it was believed that she had underlying bronchopneumonia of the left lung. Because of the recurrent episodes of pulmonary involvement sulfonamides and penicillin were administered. Aspiration of the left pleural cavity yielded straw colored fluid. Except for a mild secondary anemia, the blood count was normal. Urinalysis was essentially negative except for traces of albumin. The phenolsulfonphthalein excretion was 50 per cent in two hours. A Mantoux test was negative. Chest roentgen-ray examination and fluoroscopy confirmed the presence of a left pleural effusion and showed an enlarged cardiac outline suggestive of pericardial effusion. A diagnosis of polyserositis was entertained. The diagnosis of acute disseminated lupus erythematosus was also suggested, particularly in view of

the eruption on the nose and cheeks. The patient gradually recovered and was discharged on September 16, 1945.

She returned on December 30, 1945 because of marked fatigue, cough and fever of two days' duration. She now appeared pale and dyspneic. A gallop rhythm was present and the heart was thought to be enlarged to the left; a systolic murmur was heard over the pulmonic area. The blood pressure was 90/0. There were signs of fluid at both lung bases. The liver was enlarged to three fingers'-breadth below the costal margin. The blood count showed a hemoglobin of 40 per cent (Sahli), 2.4 million erythrocytes, 18,600 leukocytes with 88 per cent polynuclears. The platelet count was 185,000 per cu. mm. Urinalysis revealed a specific gravity of 1.012, four plus albumin, many granular casts and occasional leukocytes and erythrocytes. On urine concentration tests the specific gravity rose to 1.028. Despite multiple transfusions the anemia persisted. The circulation time was 17 seconds (saccharin) and the venous pressure 18 cm. of water. Following therapy with mercupurin and digitalis the circulation time and venous pressure returned to normal. Ten days after admission she complained of pain in the left popliteal fossa and a positive Homan's sign was obtained on the left. The temperature rose to 103.5° F. and the leukocyte count to 22,000 per cu. mm. This was followed by tenderness in the right calf and abdomen. Edema of both legs developed and the superficial veins of the abdomen became dilated suggesting inferior vena cava obstruction. A blood urea nitrogen of 41 mg. per cent was thought to indicate renal vein involvement. The diagnosis of migrating thrombophlebitis was now made. Subsequently, thrombophlebitis appeared in the upper extremities and at this time ascites was pronounced, necessitating repeated paracentesis. The edema of the lower extremities became so severe that Southey tubes were inserted. In turn, the veins of the head, face, neck and chest became dilated and many of the dilated abdominal veins were found to be thrombosed. Bilateral pleural effusion persisted. There was now pitting edema of the skin from the ankles to the clavicles. Although the urea nitrogen had previously been elevated, blood chemical studies were now all within normal limits. A Congo red test, the cephalin flocculation test, blood proteins and cholesterol were all normal. Repeated electrocardiograms showed right axis deviation with a low QRS complex in all leads; the latter was interpreted as consistent with the presence of pleural effusion. The temperature rose suddenly on May 10 to 102.4° F. and signs of consolidation were present in the left lower lobe. The patient died on May 11, 1946.

*Pathological Findings.* The essential gross anatomical alterations were as follows: There was generalized edema sparing the upper extremities. The veins of the panniculus adiposus of the abdomen were filled with fresh, red thrombi. The abdomen contained 1500 c.c. of clear, amber colored fluid. The small and large bowel were edematous and congested. The esophageal veins were dilated. The mesentery was edematous and the veins filled with grayish-white adherent and scattered red non-adherent thrombi. The liver was congested and fatty. The portal and splenic veins were occluded by a pale, yellow-gray, firm thrombus. The spleen was absent. The kidneys were congested and the renal and adrenal veins were occluded by firm, organizing thrombus extending from the inferior vena cava. The adrenal glands were grossly not abnormal. The inferior vena cava was completely filled by a firm, gray-white, organizing thrombus which extended from below the hepatic veins into the common iliac and femoral vessels. The superior vena cava and innominate veins were also filled with thrombus which was firm, gray, adherent and contained yellowish pigment. The pericardial layers were fused by filmy, fibrous adhesions. There was pronounced hypertrophy and dilatation of the right auricle and ventricle. Several small, firm thrombi were found in the right auricular appendage. The left ventricle was contracted and not hypertrophied. The valves and coronary arteries were normal. The pleural spaces were obliterated by filmy, fibrous adhesions containing fluid. The

lungs were firm, relatively airless and edematous. The small pulmonary arteries were quite prominent. The larger pulmonary arteries contained atheromatous deposits and some branches were obliterated by organized thrombi. The pulmonary veins were normal. The systemic arteries were normal.

Histologic examination revealed thrombi in various stages of organization in the involved veins. There was marked congestion of the intestines, stomach, liver, adrenal glands and kidneys. The heart showed incipient organization of the auricular mural thrombus. The most striking findings were limited to the lungs. Multiple sections showed numerous pulmonary arterioles with recanalized, organized emboli. Other branch vessels showed intimal hyperplasia. The alveoli were filled with edema fluid. There were scattered scarred areas probably representing old, organized infarcts.

*Case 5.* A white male of 16 was first admitted to the Medical Service of Dr. Eli Moschkowitz on April 14, 1941 because of purpura. His past history revealed diphtheria at the age of two, pneumonia at five, and an episode of joint pains at 12. For one year prior to admission he had noticed easy bruising and was observed at another hospital where a positive Wassermann reaction was obtained. Five weeks before admission he had measles. Following recovery he had several epistaxes and noticed that his gums bled easily when he brushed his teeth.

On examination there were numerous petechiae, purpuric spots and ecchymoses all over the body. There was generalized lymphadenopathy, although the nodes were not very large. The spleen was palpated three fingers' breadth below the costal margin. The blood count was: hemoglobin 91 per cent (Sahli), erythrocytes 5.2 million, leukocytes 6,100 with a normal differential. The blood platelets were reduced to 5,000 per cu. mm. The bleeding time was more than 20 minutes and the clotting time 16. There was no clot retraction in 24 hours. A tourniquet test was positive. A positive Wassermann reaction was obtained. The blood chemical studies were within normal limits. Urinalysis revealed a trace of albumin and occasional erythrocytes. A diagnosis of idiopathic thrombocytopenic purpura was made. However, it was thought that the disease might have been related to his measles and inasmuch as such conditions had been known to regress spontaneously splenectomy was not advised. Following therapy with snake venom the platelet count rose to 40,000 per cu. mm., the spleen receded to the costal margin and the purpura faded. He was discharged on May 26, 1941. When seen in the follow-up clinic during the next six months he appeared well. A platelet count on one occasion was 160,000 per cu. mm.

One year later, on January 5, 1942, he was readmitted because of pain in the right lower chest, cough and fever. Examination at this time revealed dullness over the right lower lobe with decreased fremitus. The spleen edge was felt. The blood pressure was 120 mm. of mercury systolic and 70 mm. diastolic. A diagnosis of acute right pleuritis was made. Fluoroscopy showed haziness over the right lung field with obliteration of the costo-phrenic sinus. A Mantoux test was negative. The clotting time was 50 minutes and the bleeding time 4; clot retraction was still quite delayed. The platelet count was 130,000 per cu. mm. Thoracentesis yielded a small amount of turbid, sanguineous fluid. Roentgenogram of the chest showed clear lung fields; the left ventricle appeared enlarged. The prothrombin time was normal. There was one to three plus albumin and microscopic hematuria on urinalysis. The temperature, which was 102° F. on admission, became normal on the following day and remained so during the remainder of his hospital stay. The clot retraction time gradually dropped to three and one-half hours, the bleeding time to three minutes and the clotting time to 20. Because of mild obesity, striae abdominalis and a blood pressure of 140/90, the diagnosis of Cushing's syndrome was suggested. Salt balance studies were negative. Subsequently, a reddish, scaling eruption was noted on the cheeks.

This finding, together with the presence of albuminuria, elevated blood pressure and unexplained pulmonary signs led to the impression that the patient might have acute disseminated lupus erythematosus. The facial eruption cleared gradually, all physical signs of pulmonary involvement disappeared and the patient was discharged as well on February 18, 1942.

He was admitted for the third time on April 1, 1942 because of nausea, anorexia, dark urine, light stools and icteric sclerae. The symptoms were of two weeks' duration. On examination he was obviously icteric. The liver was palpated two fingers' breadth below the costal margin; the spleen edge was readily palpable. The urine contained bile. Bleeding and clotting time were normal. The cephalin flocculation test was four plus. A diagnosis of infectious hepatitis was made. On the fourth day of hospitalization the patient had a marked diuresis and concomitantly the icterus began to clear. He was discharged on April 23, 1942 free of icterus and well. Between June 1942 and May 1945 he was seen in the follow-up clinic on a number of occasions and except for the complaint of occasional pain in the epigastrium and in the lower extremities he was symptom free.

On November 26, 1945 he was admitted for the fourth time to the Medical Service of Dr. Isidore Snapper because of pain along the posterior aspect of the left leg and thigh which began five weeks previously while climbing stairs. Several weeks later the pain was sufficiently severe to require bed rest and subsequently the left leg became swollen. There was no purpura. On examination a systolic murmur was heard over the fourth left interspace, along the sternal border. The liver was palpated two fingers' breadth below the costal margin and the spleen edge was just palpable. The left leg was swollen, tender and warm. A diagnosis of thrombophlebitis was made. Fluoroscopy revealed enlargement of the left ventricle and a prominent pulmonary conus. The diagnosis of diffuse vascular disease was also suggested. The fundal vessels were only slightly narrowed. The blood count was normal. Although the Wassermann reaction varied from one to three plus this was not considered significant inasmuch as similar false positive Wassermann reactions are observed occasionally in various forms of thrombocytopenic purpura. The erythrocyte sedimentation rate was 66 mm. per hour (Westergren). A sternal marrow smear was normal. The platelet count was 200,000 per cu. mm. The temperature fluctuated between 100.5° and 101.5° F. Eight days after admission he complained of severe pain in the right upper abdomen, associated with nausea. The temperature rose to 104° F. Stool guaiac test was negative. The abdominal pain persisted and the patient gradually became confused, disoriented, cyanotic, irrational and finally lapsed into a stupor. The consulting neurologists made a diagnosis of generalized encephalopathy without focal signs. Blood chemical studies were within normal limits. The leukocyte count rose to 11,000 per cu. mm. The patient died on December 12, 1945, eight days after the onset of abdominal pain, the cause of death remaining obscure.

*Pathological Findings.* The significant gross anatomical changes were as follows: The left lower extremity was moderately edematous. The left femoral vein was completely occluded by a firm, gray thrombus at a point below Poupart's ligament. Below this the vein was free and dilated. The left calf veins were filled with dark red thrombi. Both adrenal veins were occluded by firm, adherent thrombi. The adrenal glands were both enlarged and together weighed 100 grams. The left adrenal gland was completely hemorrhagic except for a narrow zone of yellow cortical tissue at the periphery. The right adrenal gland was somewhat larger than the left and likewise replaced by dark red tissue, the center of which was composed of fluid blood. There were remnants of cortical tissue at the periphery. The liver was normal in size and yellowish. The spleen was firm, weighed 400 grams and the follicles were prominent. The kidneys, stomach and intestines were moderately congested. There were firm pleural adhesions over the right lower lobe and a fibrinous pleuritis was

present over the left lower lobe. A recent infarct was noted in the left lower lobe. At the right base there was a fibrous scar and the corresponding artery contained an organized embolus. The heart was normal in size. There was a small, calcified thrombotic mass in the right auricular appendage. The remaining organs were normal. No other veins were found to contain thrombi and the systemic arteries were normal.

On microscopic examination both adrenal glands showed diffuse hemorrhagic necrosis with some fibroblastic connective tissue proliferation in the periadrenal tissues. The veins were filled with organized thrombi; the arteries were free. The femoral and calf veins were occluded by thrombi in various stages of organization and recanalization. The heart muscle contained small foci of acute necrosis. No vascular changes were seen in the heart. Within the right atrium there was a calcified, organized mass of tissue attached to the mural endocardium. The right lower lobe showed an area of connective tissue organization of the parenchyma and the corresponding artery contained a recanalized thrombus. Many small pulmonary artery branches contained thrombi. In the left lower lobe there was a recent area of hemorrhagic necrosis. The liver showed widespread foci of liver cell necrosis. There was a pronounced infiltration of the portal fields by round cells and occasional miliary granulomata were present. Many of the medium and small hepatic veins showed a round cell and polynuclear infiltration of the wall. No thrombi were present in either the portal or hepatic veins. The spleen showed intense hyperemia and large follicles with prominent germinal centers. The remaining organs did not reveal any significant changes on histologic examination.

*Case 6.* A 35 year old, white truck driver was admitted to the Medical Service of Dr. George Baehr on February 23, 1946 complaining of right upper quadrant pain. Two and one-half years prior to this admission he had had an episode of swelling of a lower extremity with ecchymosis in the popliteal region. When this had subsided the opposite side had become involved and then also subsided. Nine months later he developed cerebral symptoms consisting of headache, faintness, transient unconsciousness and paralysis of the left arm and leg of one hour's duration. Complete neurological investigation at another hospital, including electroencephalogram and pneumoencephalogram, was negative. Six months prior to his admission to The Mount Sinai Hospital he had a shaking chill with fever to 102° F. and a mild cough productive of blood-flecked sputum. These symptoms persisted for a month. Three months later he had a recurrence of ankle and leg swelling with popliteal ecchymosis alternately involving each leg. Three weeks before admission he had hemorrhages in both sclerae followed by hematuria, cramping lower abdominal pain, persistently bloody stools and transient swelling of the neck with dysphagia of one day's duration. He vomited on several occasions.

On examination the temperature was 99.4° F., pulse 100 per minute, respirations 22 per minute, and the blood pressure 140/80. Two hemorrhages were found in the right sclera, the liver was palpable 5 cm. below the costal margin and the tip of the spleen was felt. Dark red blood was found in the rectum. Several ecchymoses were present at the site of needle puncture wounds. An exhaustive hematological examination had been done prior to hospital admission by Dr. Nathan Rosenthal and was reported as follows: Hemoglobin 75 per cent (Sahli), 5.02 million erythrocytes, 10,200 leukocytes with a normal differential count and 40,000 platelets. The bleeding time was three minutes and clotting time five. Clot retraction was normal and the tourniquet test positive. Prothrombin index was 81 per cent. Bone marrow smear was essentially negative except for lack of fragmentation of platelets. The hemoglobin on admission had fallen to 45 per cent (Sahli). The urine contained numerous red blood cells. The stool gave a four plus guaiac reaction. The brom-sulfalein test showed 12 per cent retention after 30 minutes. The blood chemical



findings were: total proteins 7.7 gm. per cent; glucose 75 mg. per cent; cholesterol 168 mg. per cent. Cephalin flocculation test was one plus. The icteric index and Van den Bergh reaction were normal. Sedimentation rate was 52 mm. per hour (Westergren). Electrocardiogram was normal. During his stay in the hospital he developed fresh purpuric spots over the chin and knees. The platelet count was consistently low. He was transfused several times without improvement. Finally, it was decided that he had thrombocytopenic purpura and that the spleen should be removed. Following splenectomy he had a chill followed by a rise in temperature to 105° F. There was a leukocytosis of 30,900 per cu. mm. and the platelet count rose to 180,000. His fever subsided and he was discharged on March 30, 1946 feeling fairly well. The pathological report on the spleen was "Histological structure is not that generally seen in thrombocytopenic purpura. There is a diffuse fibrosis of the splenic pulp, together with intrasplenic phlebosclerosis and obliterating endophlebitis such as is seen in obstructive splenomegaly."

Two weeks later, on April 18, 1946, he was readmitted because of cramping abdominal pain, vomiting and melena. This had been preceded by transient left chest pain, fever to 101° F. and anorexia. Examination on this admission revealed a hemorrhagic folliculitis of the neck, petechial hemorrhages of the feet and a hemorrhagic bleb on the left buttock. Hematological study by Dr. Nathan Rosenthal on the day before this admission revealed: Hemoglobin 70 per cent (Sahli); 4.3 million erythrocytes; 12,400 leukocytes with a differential count of 50 per cent segmented, 7 per cent non-segmented, and 5 per cent eosinophilic polynuclears, 28 per cent lymphocytes and 8 per cent monocytes; platelets 40,000 per cu. mm.; hematocrit 41 per cent; icteric index 3. Bone marrow smears were normal. The formol gel test was negative and cephalin flocculation one plus. The urine on repeated examination showed albumin varying from 1 to 3 plus, and erythrocytes and leukocytes from time to time. All liver function tests and blood chemical findings were within normal limits. The electrocardiogram was normal. Roentgenologic study showed the presence of esophageal varices; the remainder of the gastrointestinal tract was normal. The electroencephalogram was normal. Intravenous and retrograde pyelography were normal. The platelet count rose progressively from 40,000 to 1,690,000 per cu. mm. two weeks after admission and then fell gradually to 55,000 two weeks later. Hematuria now reappeared and bright red blood was seen in the stool demonstrated by anoscopy to arise from dilated hemorrhoidal veins. Because of the cyclic character of his symptoms blood estrogen studies were done with negative results. The hematuria gradually subsided, the platelet count rose to 310,000 per cu. mm. and the patient showed progressive improvement following administration of iron and several transfusions. He left the hospital on June 1, 1946.

Following discharge he had recurrent episodes of bleeding characterized by hemorrhagic folliculitis and tarry stools. He also had cough with scanty hemoptysis and on one occasion non-radiating precordial pain for one week. Two days before his third admission on September 28, 1946 he developed hemorrhagic "pimples" of the face, left-sided headache and alternating aphasia and lucidity. Examination revealed that he was acutely ill with a temperature of 102° F. Several petechiae were seen in the left conjunctiva and there was blurring of both discs. A short apical systolic murmur and a split second sound were heard. Cyanosis of the fingers and toes was evident. The deep reflexes were equal and hyperactive. Slight nuchal rigidity was present, but the Kernig and Brudzinski signs were negative. He had motor aphasia with perseveration. Lumbar puncture showed a spinal fluid pressure of 210 mm. of water and microscopically there were 10 erythrocytes per cu. mm. Xanthochromia was not present. Subsequently, a right Babinski sign, increased reflexes of the right lower extremity and progressive bradycardia suggested the diagnosis of subdural hematoma and craniotomy was advised. Three days after



admission a decompression was done. On October 10 a ventriculogram revealed a dilated ventricular system involving the anterior horn of the left lateral ventricle and a shift of both ventricles to the right, suggestive of a mass in the left temporal lobe. At operation a hematoma was found in the anterior portion of the left temporal lobe and the blood clot was evacuated.

He recovered from the effects of the operation except for aphasia and on October 16 was transferred to the medical ward for further study. Complete blood chemical study and liver function tests were normal. Except for left axis deviation the electrocardiographic findings were normal. Urinalysis was now negative except for the occasional presence of leukocytes and erythrocytes. The platelet count waxed and waned, varying from 565,000 to 75,000 per cu. mm. Purpura appeared again on November 5 when the platelet count was 85,000 per cu. mm. Four days later phlebitis of the right lower extremity was observed and two days thereafter the platelet count was found to be 480,000 per cu. mm. The bleeding and clotting time and the clot retraction time were now normal. However, on November 13 the platelets again fell to 75,000 per cu. mm. only to rise again on November 18 to 385,000 per cu. mm. On November 23 the platelets fell to 100,000 per cu. mm. The stool was now guaiac positive and purpura appeared on the face. Dicoumarol therapy was suggested because of the phlebitis but was considered dangerous in view of the recurrent drop in platelet count with purpura. On December 5 tenderness developed in the right calf with a leukocytosis of 18,150 and a platelet count of 275,000 per cu. mm.; bleeding and clotting time were normal. He was discharged on December 8 when all symptoms had subsided with the diagnosis of visceral thrombophlebitis migrans, cavernomatous transformation of the portal vein and reactive purpura due to the withdrawal of platelets into the venous thrombi. On January 11, 1947, while in his physician's office, he died suddenly.

*Pathological Findings.* The essential gross findings were as follows: There were well healed left temporal craniotomy and left upper abdominal scars. The right lower extremity was edematous. Petechiae were present over the lower extremities and trunk. The superficial veins were dilated. There was no free fluid in the abdomen. The major proximal portion of the splenic vein, the extrahepatic portion of the portal vein and the superior mesenteric vein and its major tributaries were completely occluded by pink-gray, porous tissue. In addition, the perivascular tissues of the portal and superior mesenteric veins were spongy and contained countless pinpoint to pinhead sized lumina. This cavernomatous transformation was most marked in the hepato-duodenal ligament which measured 3.5 cm. in thickness. The spleen was absent. The liver was somewhat increased in size. The adhesions between the diaphragm and the superior surface of the liver were highly vascularized. The cut surface of the liver was reddish brown and the lobular pattern preserved. The portal fields were in some areas replaced by spongy, vascular tissue. In other areas, the portal vein could be identified and contained fresh and organizing thrombi. Similarly, the radicles of the hepatic veins were filled with thrombi. Some of the larger hepatic veins showed recanalized thrombosis. The mesentery of the small intestine also showed evidence of cavernomatous transformation, less in extent than that noted in the hepato-duodenal ligament. The esophageal veins were dilated. The remainder of the intestinal tract was merely congested with scattered ecchymotic areas in the mucosa. The hemorrhoidal veins were dilated. The right common iliac vein was completely occluded by a firm, gray-red thrombus which extended for a short distance into the inferior vena cava and across into the left common iliac vein. There was a massive embolus in the right ventricle extending into the main pulmonary artery and into the left main branch. The heart was otherwise normal. The right lower lobe contained one recent and one organizing infarct. The pulmonary artery branches to the right lower lobe contained firm emboli. The lungs otherwise

were only mildly congested. The remaining organs, aside from congestion, revealed nothing noteworthy.

On microscopic examination the veins of the portal system contained organized and recanalized thromboses with areas of acute inflammation with polynuclear leukocytes many of which were eosinophiles. In the areas of acute inflammation the elastica interna of the veins showed focal fragmentation. Sections of the porta hepatis and mesentery of the small intestine showed cavernomatous transformation. Many of the channels were thrombosed and there was considerable surrounding acute inflammatory reaction with many eosinophilic leukocytes. The right common iliac vein contained a recent and an old organizing thrombus. Scattered accumulations of lymphocytes were noted in the adventitia and surrounding connective tissue. The lungs presented organizing infarcts with fresh and organized emboli in the involved pulmonary arteries. Sections of the liver revealed extensive changes in the portal and hepatic veins consisting of the presence of recent thrombi, organizing and recanalized thrombi, cavernomatous transformation of many portal fields and acute inflammation of scattered hepatic and portal veins. Many eosinophiles were present in the inflammatory exudate. Some of the inflamed veins did not contain thrombi. The liver cells showed only slight fatty change. The veins of the gall-bladder revealed acute inflammation without thrombi; here also, eosinophiles were present. There was interstitial edema of the kidneys and occasional large renal vein branches contained recanalized thrombi. Section of the bone marrow showed normal cellular elements including megakaryocytes with numerous eosinophilic myelocytes. The remaining organs were congested.

## DISCUSSION

Idiopathic migratory thrombophlebitis is distinct from other forms of vein inflammation. It is well known that thrombophlebitis may appear in various conditions in which there is injury to the vein wall. Such injury may be mechanical, chemical or bacterial. In addition, any factor producing stasis favors the development of thrombophlebitis. Neoplasms may cause local thrombosis and in some cases unexplained peripheral thrombosis, as in carcinoma of the pancreas. Schlagenhauser<sup>10</sup> described perivenous lymphatic tumor infiltration of the veins of the arms in a patient with primary carcinoma of the stomach. Changes in the properties of the blood which occur in various diseases may produce thromboses of veins. Thus, in nephrosis where there is an increase in blood fibrinogen thromboses may occur and they may also be found in a variety of so-called cachectic states. In any condition associated with thrombocythemia thromboses may occur spontaneously in veins. This is found in polycythemia vera, in idiopathic thrombocythemia, in megakaryocytic aleukemic myelosis and in the transient thrombocythemia following splenectomy. It is important to emphasize that in our cases none of these conditions was present and that the disease was produced by an unknown systemic factor causing thrombosis and inflammation of veins in scattered locations throughout the body.

Migratory phlebitis may be associated with thromboangiitis obliterans. The vein involvement is usually superficial and peripheral and the visceral veins are generally spared. Baehr and Klemperer<sup>11</sup> reported recurrent portal and splenic vein thrombosis with death due to mesenteric vein throm-

bosis in a male with a long history of Buerger's disease. The venous affliction often precedes the arteritis<sup>12</sup> at times by many years. However, there is usually symptomatic as well as objective evidence of associated arterial disease at some time. In none of our cases was such evidence of arterial involvement found.

Idiopathic migratory phlebitis affects both peripheral and visceral veins in a haphazard fashion. The degree, duration and distribution of the venous affection are variable. As a rule, the disease is characterized by involvement of short segments of medium and small sized vessels. This is particularly true in cases without visceral vein lesions. In the more severe forms, however, long segments or complete venous systems may be involved with sequelae dependent upon the venous system attacked. More commonly, the veins of the lower extremities are affected and the inflammation wanders from vein to vein and from one extremity to the other. At times, the veins of the upper extremities and neck are implicated. The majority of cases are benign with localization of the disease process to the veins of the upper and lower extremities and occasional lesions in the visceral veins. The disease tends to subside spontaneously in periods varying from several weeks to months. It may recur within several months or even years later. Generally, the thrombi in the affected veins undergo organization and recanalization and except for minor sequelae, such as postural edema when the lower extremities are involved, there are no residua. Even those patients with occasional lesions in the visceral veins may go on to complete healing. In those cases with more extensive involvement of the veins, especially of the viscera, the disease appears to have an acceleration not seen in the ordinary forms of peripheral migrating phlebitis. Many cases of visceral migratory phlebitis, however, even those which end fatally, may begin with thrombophlebitis of the legs indistinguishable from other types of nonbacterial thrombophlebitis due to known causes.

There are no pathological features which permit specific characterization of migratory thrombophlebitis as either venous or perivenous in origin. Both types of inflammation are seen and the degree varies from case to case. It is uncertain whether the endothelial and intimal alterations, as well as the changes in the vein wall, are secondary to thrombosis or the result of a primary process. The inflammatory exudate is predominantly polynuclear in the acute stages and lymphocytic and monocytic in the later stages. Eosinophilic infiltration may also be seen (Case 6).<sup>7,13</sup> At times the inflammation extends into the perivenous tissues. Granulomatous inflammation with giant cells has been described in peripheral migratory thrombophlebitis, both with<sup>12</sup> and without<sup>14,15</sup> associated thromboangiitis obliterans. This type of inflammation has not been observed in the visceral forms of the disease. Organization of thrombi and recanalization of veins may occur together with acute thrombophlebitis, especially in protracted cases. Histologically, idiopathic thrombophlebitis cannot be distinguished from traumatic, static or other nonbacterial forms.

The changes in the visceral veins and venae cavae do not differ from those in the peripheral vessels. Disordered function of organs, however, is dependent upon the degree and duration of the thrombophlebitis of the corresponding veins, among other factors. Thus, practically every organ in the body may be affected in this disease. Since the visceral alterations vary considerably from case to case, the protean clinical manifestations are often unclear until postmortem examination.

The presence or absence of damage to the tissue drained by the involved vein depends upon the degree of occlusion and recanalization, the extent of the collateral venous circulation and other factors. Congestion with or without hemorrhage is the rule and edema or serous effusion may occur in severe cases. Infarction is uncommon and has been observed in this disease only in the intestine and in the adrenal glands. In the bowel, secondary ileus and arterial spasm may be factors in obstructing the circulation, whereas in the adrenal gland collateral circulation is poor and intracapsular hemorrhage may produce pressure necrosis. Infarction of the lung is of course arterial and embolic and only an indirect consequence of thrombophlebitis. A consideration of the pathological and functional changes in the viscera in the present cases and in those reported by others will clarify some of the clinical phenomena that may be encountered.

*Lungs.* Pulmonary symptoms may often precede the demonstrable presence of phlebitis (Cases 3, 4, 5).<sup>16</sup> The presenting symptoms may be chest pain followed by pleural effusion associated with cough and at times blood-tinged expectoration. The diagnosis of either idiopathic pleurisy with effusion or bronchopneumonia is usually entertained. Only the subsequent appearance of peripheral phlebitis suggests the presence of pulmonary infarction. Pulmonary vein lesions were not found in any of our cases nor in any of the reported autopsied cases. The clinical diagnosis of pulmonary phlebitis made by several authors<sup>17, 18, 19, 20</sup> seems untenable. The pulmonary signs were most probably due to infarction either from silent or clinically apparent peripheral or visceral phlebitis.

Pulmonary embolism may also be silent and may occur without infarction, especially in the healthy lung. On the other hand, the embolus may be massive and the immediate cause of death (Case 6).<sup>6</sup> Repeated pulmonary embolism may produce such extensive obstruction of the smaller arteries, with or without associated infarcts, as to cause pulmonary hypertension and cor pulmonale with terminal right heart failure (Case 4).

*Heart.* Thrombophlebitis of the coronary venous system was observed neither in our cases nor in the other autopsied cases. The diagnosis has been made clinically, however, by several authors,<sup>18, 19</sup> the symptoms being suggestive of coronary artery occlusion although electrocardiographic changes were absent. Transient arrhythmias have also been observed.<sup>18</sup> It is difficult in these cases to exclude the factor of coronary insufficiency secondary to pulmonary embolization. Acute or chronic cor pulmonale has already been discussed. Thrombosis of the auricular appendage occurred in

Case 5 and may have been responsible for pulmonary embolization during the course of the illness.

Thrombosis of both main venous conduits to the heart, the superior and inferior vena cava, may produce obstructive venous congestion and forward or hypodiastolic failure very similar to that seen in constrictive pericarditis. This is well exemplified by Case 2.

*Liver.* Either of the two venous systems of the liver may be affected. Parietal thrombi may be found in the hepatic veins either independently (Case 6) or extending from inferior vena cava thrombophlebitis (Case 2). More extensive hepatic vein occlusion and corresponding marked hepatic enlargement with ascites has been reported clinically<sup>21</sup> but was not found in our cases. In Case 5, multiple foci of hepatic vein inflammation without thrombosis were found in the substance of the liver.

Portal vein thrombosis occurred in three of our cases and in one of the other autopsied cases.<sup>3</sup> When the thrombus is parietal the lesion is no different from that seen in other large veins. Ascites is a common manifestation of more complete occlusion of the portal vein (Cases 4 and 6). Organization of the thrombi with multiple recurrences of the inflammatory process may lead to extensive collateral venous channels which again may be involved in the recurrent disease. In one of our cases (Case 6) and in one of the reported autopsied cases<sup>3</sup> cavernomatous transformation of the hepato-duodenal ligament was produced with numerous tiny collateral venous channels carrying blood to the liver in place of the obstructed portal vein. Portal thrombosis is also associated with dilatation of the collateral channels into the caval system (esophageal, gastric, umbilical, retroperitoneal, hemorrhoidal, etc.) as seen in cirrhosis of the liver. Occasionally, hematemesis and melena may occur. It is of interest that no clinically significant alterations in liver function were found in cases of portal or hepatic vein thrombosis.

*Spleen.* Lesions of the splenic vein in migratory thrombophlebitis were associated with either mesenteric<sup>7</sup> or portal thrombophlebitis. In Cases 1 and 4 widespread thrombosis of the splenic vein occurred terminally. When the disease is chronic in the portal or splenic veins, the spleen enlarges and the pathologic features are those of congestive splenomegaly (Case 6).

*Intestines.* The most common visceral veins involved in migratory thrombophlebitis are the mesenteric (Cases 1, 4 and 6).<sup>3, 5, 7, 13, 18, 19, 20, 22, 23, 24</sup> The symptoms are generally those of abdominal pain, fever, distention, leukocytosis and at times prostration. Vomiting and frank melena or guaiac positive stools are common. Although many patients recover spontaneously, mesenteric vein thrombosis was the cause of death in a number of instances<sup>3, 5, 7, 13</sup> and in Case 1 of this series. In the fatal cases many of the abdominal veins are affected, including the portal, gastric, splenic and mesenteric. Infarction of the bowel, as seen at post mortem, is usually extensive. However, occlusion of the mesenteric veins with suggilation and bleeding may occur with eventual complete recovery.

*Kidneys.* Thrombophlebitis of the renal veins was observed in a number of instances. When the occlusion was incomplete there was little occasion to suspect renal involvement (Cases 1, 2, 4 and 6),<sup>6</sup> even in the presence of moderate albuminuria. In Case 3, however, the migratory thrombophlebitis had already apparently subsided, following extensive visceral vein thrombosis. Recovery was attended by organization of the thrombi with partial recanalization of the inferior vena cava and both renal veins. Obstruction to the renal venous flow was sufficient, however, to produce pronounced renal congestion and persistent severe albuminuria. The patient then appeared with hypoproteinemia, hypercholesterolemia and anasarca, representing the full blown syndrome of lipoid nephrosis. This is the second recorded case<sup>34</sup> of the development of lipoid nephrosis as a result of chronic renal venous obstruction.

*Adrenal Glands.* - Thrombophlebitis of the adrenal veins was not observed in the five autopsied cases of migratory thrombophlebitis previously reported in the literature, nor has clinical involvement of these organs been described. In three of the six cases reported here there were adrenal vein thrombi. In Case 1 there were parietal thrombi in both adrenal veins; in Case 3 the left adrenal vein was almost completely occluded. No significant histological organ changes were found in either instance. Both adrenal veins were completely occluded, however, in Case 5 and both glands were the seat of hemorrhagic infarction. The terminal clinical findings were those of abdominal pain, nausea, sudden rise in temperature to 104° F., followed by confusion, disorientation, cyanosis, stupor and death eight days after the onset of symptoms.

*Central Nervous System.* There are eight case reports in the literature in which cerebral symptoms are described during the course of migratory thrombophlebitis.<sup>3, 4, 17, 24, 25, 26, 27, 28</sup> All but three of the patients recovered. No autopsy was performed in one of the fatal cases<sup>26</sup>; in another the brain was not examined at post mortem,<sup>3</sup> thrombosis of the jugular veins and cerebral sinuses was the cause of death in the third.<sup>4</sup> The symptoms included transient aphasia, weakness and incoördination of one or the other of the upper extremities and hemiplegia. Erlenmeyer<sup>24</sup> mentions involvement of the cerebral sinuses as evidenced by edema of the eyelids and face, followed by delirium, unconsciousness and focal signs of central nervous system involvement. Bucy and Lesemann<sup>25</sup> reported an instance of retinal and cerebral vein thrombosis, the latter confirmed at operation performed because of the diagnosis of subdural hemorrhage. The patient also had recurrent thrombophlebitis of the lower extremities and finally recovered. Cerebral symptoms were present in Cases 2 and 6 of this report. Unfortunately, the brain was not examined at post mortem in either instance. The symptoms, however, were not unlike those reported in the literature and probably were caused by thrombophlebitis of the cerebral veins or sinuses.

In addition to those manifestations of thrombophlebitis which are attributable to injury to a specific organ in which the venous drainage has

been obstructed, there are several systemic manifestations related to the disease itself. One of these is fever. This is very common in acute thrombophlebitis whether or not there is any injury to the organ drained by the particular vein involved. It is, for example, commonly seen in peripheral thrombophlebitis and is presumably due to the inflammation of the vein wall and surrounding tissues. The fever is rarely pronounced and in no way characteristic. It is often associated with leukocytosis, sometimes to levels as high as 20,000 or 30,000 cells per cubic millimeter, but usually not exceeding 15,000. In Cases 2 and 6 and in several reported in the literature<sup>7, 13</sup> there was an eosinophilia varying from a moderate increase in eosinophiles to differential counts above 25 per cent. The reason for this eosinophilia is quite obscure. It may be mentioned again that the inflammatory exudate in the veins in some cases contained a considerable number of eosinophiles. The sedimentation rate is also frequently increased, especially if the thrombophlebitis is acute and is associated with other manifestations of inflammation such as fever and leukocytosis.

Anemia is also seen in thrombophlebitis, but here it is often difficult to estimate the significance of the nutritional factor. It is possible that the toxemia associated with the inflammatory reaction depresses bone marrow function in some cases. It is doubtful whether significant amounts of blood are withdrawn from the circulation into the thrombi. In the presence of thrombocytopenia, anemia may, of course, be secondary to purpura.

One of the most interesting relationships in this disease is that between thrombocytopenic purpura and the thrombophlebitis. It is surely no accident that of the six fatal cases of this disease which are reported here, three were in some way associated with thrombocytopenic purpura. In Case 6, the thrombophlebitis antedated the thrombocytopenia. In this case, the purpura was uninfluenced by splenectomy and the platelet count fluctuated in a cyclic fashion, possibly because of recurrent scattered thromboses. It is possible that the purpura here was caused by a withdrawal of platelets into the thrombi, as has been postulated in so-called acute febrile anemia with purpura.<sup>29, 30</sup> There was no depression of megakaryocytes in the bone marrow and it is therefore difficult to explain this purpura in any other way. Also in this patient, the hemorrhagic manifestations of purpura were interspersed with those of thrombophlebitis. In the other two cases, the purpura preceded the clinical evidence of thrombophlebitis. In Case 4, the phlebitis appeared long after splenectomy for purpura and was not associated with thrombocytosis. In Case 5, the thrombophlebitis also appeared long after the purpura had subsided, this time without splenectomy and again was not caused by a thrombocytosis. It is to be emphasized that in none of these cases was the thrombophlebitis a manifestation of post-splenectomy thrombocythemia as described by Rosenthal<sup>31</sup> and Klemperer.<sup>32</sup> Whether thrombocytopenic purpura alters the clotting mechanism of the blood in some way as yet unexplained and favors the subsequent appearance of thrombophlebitis, is a subject for conjecture.

The pathogenesis of thrombophlebitis migrans remains completely unclear. The factor of bacterial infection of the veins can be safely excluded. Whether these inflammatory reactions in the veins can be attributed to a systemic toxin or to a virus which becomes selectively localized in the veins has not been determined. It is also possible that the lesions are due primarily to a thrombosis of a vein, the reaction in the blood vessel being of a secondary character. Some change in the clotting mechanism of the blood, such as an increase in thromboplastin, might produce thromboses in scattered veins throughout the body. Changes in the clotting properties of the blood are certainly concerned with the character of the thrombi and their propagation once they are formed, whatever the initiating cause. It is clear, however, that the actual etiology of thrombophlebitis migrans continues to remain unknown.

There is no known specific treatment for migrating thrombophlebitis. When the disease is complicated by the occurrence of repeated pulmonary embolization, the question of ligation of peripheral veins may arise. The administration of anticoagulants, such as heparin and dicoumarol, might well affect the course of the disease. Recently, the use of sodium tetrathionate has been advocated.<sup>33</sup> No conclusive evidence has as yet been presented of the efficacy of any of these therapeutic measures. Inasmuch as recovery in thrombophlebitis migrans is common, nonspecific supportive therapy should always be maintained.

### SUMMARY

Although involvement of the visceral veins with recovery is not uncommon in thrombophlebitis migrans, the disease may be fatal.

The clinical features and pathological changes in 11 autopsied cases are reviewed. Of these, six are reported by us and five collected from the literature.

The protean clinical manifestations caused by involvement of various organs as well as the complex systemic features of the disease are described.

Pathogenesis remains obscure and therapy is limited.

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# THE CONDITIONED REFLEX TREATMENT OF CHRONIC ALCOHOLISM. X. AN ANALY- SIS OF 3125 ADMISSIONS OVER A PE- RIOD OF TEN AND A HALF YEARS \*

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FROM the time this institution was founded in 1935 until the end of 1945, a period of ten and a half years, 3125 patients had been admitted for the treatment of chronic alcoholism. These patients received no definitive treatment for their addiction except conditioning therapy. The technic of this therapy has been reported previously.<sup>1, 2, 3</sup> Those admitted subsequent to 1940 received the benefit of reinforcement.<sup>4</sup> Reinforcement consists of periodic return for a single conditioning seance during the year following the completion of initial therapy. This was designed to maintain the conditioned reflex at its optimum level for the first 12 months during which time it had been shown<sup>1</sup> the majority of relapses occurred.

The patients to be reported were unselected. Treatment was never refused an applicant except for physical disability or because of the presence of psychotic manifestations or obvious insincerity.

During the war years our curtailed clerical and field staffs found it impossible to maintain current records. As a consequence this survey, begun at the end of 1945, is just now being reported. The status of each patient is reported as of the closing date of the survey, that is, at the end of 1945. Individual data were secured by personal contact in all instances except those patients living east of the Mississippi River. In the latter cases, written replies known to be reliable were accepted. Unless current and accurate information was to be had, the patient was counted as unknown.

Other analytical data were taken from the hospital records. While not complete in all instances, a sufficient number of patients are included in most groups considered to render the figures statistically significant.

## ESTABLISHING THE NET CASES

Of the 3125 patients admitted 304 were not given treatment. The reason for failure to give treatment was not shown on the record of 86 cases. After disintoxication 135 patients refused to take treatment, believing they were not alcoholics and therefore in no need of assistance. Treatment was not given to 13 patients because of psychotic manifestations or obvious insincerity and to 32 patients because of physical disability. Thirty-

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one patients refused to complete the prescribed course of therapy and left the hospital against advice. Deaths in this series numbered 7. Of these, three were considered to be the result of treatment, one being due to congestive heart failure and two resulting from coronary occlusion. Two patients died of delirium tremens after treatment had been started and two succumbed to delirium during disintoxication. Unknown cases numbered 448. Also classified as unknown were 50 patients who had died prior to the closing date of the survey. Even though these patients were abstinent at the time of their deaths they were, of necessity, counted as unknown for it was impossible to state whether they would have remained sober had they lived. On the other hand, patients who relapsed and later died were listed as relapses for statistical purposes.

The net cases of the series, that is, those treated whose status was definitely known on the closing date of the survey, therefore, numbered 2323. The tabulated data are presented in table 1.

TABLE I  
Summary of Cases Excluded from Consideration

Not treated		
reason not stated on record	86	}
patient refused treatment	135	
treatment refused patient	13	
physical disability	32	
refused to complete treatment	31	
died during disintoxication	2	
died during treatment	3	
died during treatment (delirium)	2	
Status unknown		448
Died abstinent prior to closing of survey		50
Net cases included in survey		2323
Total admissions		3125

#### ABSTINENCE AMONG THE NET CASES

Complete and continuous abstention from alcohol in any form between the time the individual was treated and the closing date of the survey was necessary in order for a patient to be classified as "abstinent."

The overall abstinence for the entire series of cases was found to be 44.8 per cent, for 1042 of the 2323 cases treated during the previous ten and a half years were found to be abstinent at the end of 1945. In addition, 92 patients of this group who relapsed and within a short time were treated a second time remained sober. If these latter patients are considered as successful cases the percentage of abstinence is 48.8 per cent. Not a few patients were treated a third or even a fourth time. Such cases were counted as relapsed even though they happened to be abstinent on the closing date of the survey.

A consideration of the overall percentage of abstinence alone, however,

does not give a fair picture of the results from conditioning therapy for it implies a higher percentage of abstinence among those treated from three to 10 years previously than was actually found to exist. If the period of the survey is divided into 21 periods of six months each it may be seen from figure 1 that the more recent groups, with the higher percentage of abstinence, contain a great many more patients than the earlier groups, thus affording a statistical advantage which tends to distort the significance of the average figure.

A truer analysis is obtained when the percentage of abstinence for each six month period is studied (figure 1). When this is done it may be safely stated that: (1) about 85 per cent of patients treated will remain abstinent for at least six months; (2) about 70 per cent will remain abstinent for one year or longer; (3) over 60 per cent will remain abstinent for two years or longer; (4) about 55 per cent will remain abstinent for three years or longer; (5) about 40 per cent will remain abstinent for four years or longer; (6) over 30 per cent will remain abstinent up to seven years or longer; and (7) about 25 per cent will remain abstinent up to ten and a half years or longer.

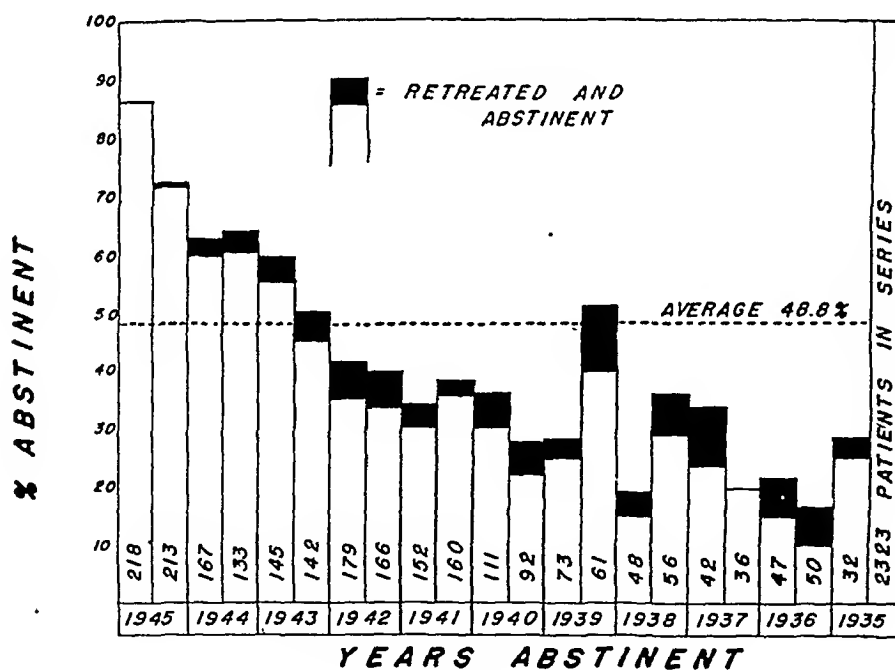


FIG. 1.

#### A CONSIDERATION OF FACTORS LIKELY TO AFFECT PROGNOSIS

A number of physical, environmental, personal and personality factors thought likely to either precipitate relapse or enhance the chances of remaining abstinent were examined statistically. It was hoped that definite information could thus be obtained to be used advantageously in gauging

the necessity for special treatment of individual cases upon admission. While incomplete in many instances the material to be considered from this point on is scattered throughout the series in approximately the same ratio as exists in the entire series. Since subsequent figures will apply only to those patients receiving treatment for the first time an evaluation of the relative importance of each factor may be had by comparing the percentage of abstinence for any given category with the overall abstinence figure of 44.8 per cent.

*The Sex of the Patient.* Ninety-three per cent of the patients were men and 7 per cent were women. Whereas, 43.9 per cent of the men remained abstinent, it was found that 46.2 per cent of the women remained abstinent. This result was somewhat surprising as our earlier observations<sup>1, 5</sup> indicated that women were somewhat less favorable subjects than men.

TABLE II  
The Relation of Age to Percentage of Abstinence

Age in Years	Cases in Group	% Abstinent
Under 20	0	—
21-25	26	23.1
26-30	139	28.7
31-35	333	38.1
36-40	466	42.5
41-45	418	48.3
46-50	325	46.5
51-55	209	50.2
56-60	118	50.8
61-65	53	52.8
66-70	8	37.5
Over 70	4	75.0

*The Age of the Patient.* Table 2 shows what appears to be a significant correlation between the age of the patient and his likelihood of remaining abstinent following therapy. Patients under 25 are poor risks as shown by an abstinence figure of 23.1 per cent for this group. The age group from 26 to 30 is but slightly better with 28.7 per cent abstinence. Patients between the ages of 31 and 35 are still considerably below the average for the entire series with a figure of 38.1 per cent. The age group 36 to 40 approaches the average for the entire series with a figure of 42.5 per cent abstinence. This age group may be considered as average so far as the age factor is considered. From this point, as the age of the patient increases, so do his chances of remaining abstinent following treatment. The patients over 65 years of age are too few in number to be evaluated with accuracy.

These data confirm our earlier observations that the younger patients are less favorable subjects for conditioning therapy alone than are those of more maturity. It is suggested that other methods of treatment should be combined with conditioning in those patients under 35 years of age.

*The Religious Belief of the Patient.* The religion of 1634 patients was shown on the record. Eighty per cent were Protestant and 20 per cent Catholic. The data show that 45.5 per cent of the Protestant group remained abstinent as compared to 43.7 per cent of the Catholics. This difference is not statistically significant. It is significant, however, that of 29 Catholic patients who were divorced at the time treatment was taken, a single case remained sober. Such a high relapse rate was not noted among Protestant patients who had been divorced (*vide infra*).

*The Patient with Family Troubles.* Marital discord appeared to have a deleterious effect for of 499 patients complaining of this situation, only 116 or 23.2 per cent remained abstinent following treatment.

*The Marital Status of the Patient.* Table 3 indicates a similar effect among patients who were separated but not divorced for only 25.6 per cent of 86 such patients remained abstinent. Patients who had been divorced prior to the time treatment was taken numbered 111; 32.4 per cent of these remained abstinent. Twenty-nine patients had been divorced and remarried; 44.8 per cent of this group remained abstinent. Sixty-one patients who were classified as widowed showed an abstinence record of 44.3 per cent. Of 292 single patients, 42.1 per cent remained abstinent. The optimal marital circumstance appeared to be among those patients who were married for the first time for 50.0 per cent of 1329 such patients remained abstinent.

TABLE III  
The Relation of Marital Status to Percentage of Abstinence

Marital Situation	Cases in Group	% Abstinent
Separated—not divorced	86	25.6
Divorced—now single	111	32.4
Single	292	42.1
Widowed	61	44.3
Divorced—remarried	29	44.8
Married (once)	1392	50.0

*The Patient's Occupation.* When classified according to the scheme shown in table 4, definite differences in the percentage of abstinence among various occupations are noted. The differences, however, do not appear to be related to educational requirements, degree of skill, social status or monetary factors, for it may be seen that the group with the highest percentage of abstinence is comprised of those of a highly skilled occupation requiring extensive educational preparation which is acceptable socially and highly paid. Yet the least successful category, that of the professional group (attorneys, physicians, dentists) is similarly characterized.

Marked differences were found to exist within individual groups between closely related occupations. As an example, abstinence among bakers was found to be 18 per cent while among cooks it was 55 per cent.

None of the occupations listed were considered to be particularly hazardous in themselves. A number of occupations, however, not ordinarily hazardous become potentially very dangerous to the intoxicated employee.

Included are such jobs as truck drivers, high riggers, electricians, painters, structural steel workers, railroad engineers, welders, etc. The percentage for such a group was found to be 53.1 per cent while in a similar size group where employee drinking did not increase the industrial hazard the rate of abstinence was only 41.4 per cent. Apparently, the factor of safeguarding his own life serves as a stimulus to abstinence.

TABLE IV  
The Relation of Occupation to Percentage of Abstinence

Occupation	Cases in Group	% Abstinent
Engineers and architects	76	63.2
Civil service employees	18	55.5
Farmers	103	55.3
Retired	15	55.3
Owner of business	252	50.4
Journalist	20	50.0
Housewife (not employed)	100	50.0
Business men	62	46.8
Unskilled worker	387	43.9
Skilled worker	630	43.6
Salesmen	130	42.3
Professional	90	39.9

If the data are analyzed according to whether the employee was engaged in a public service occupation (barber, retail clerk, cab driver, salesman, waiter, etc.) it was found that 45.6 per cent of this group remained abstinent after treatment while 49.2 per cent of those whose occupation did not require contact with the public remained abstinent. While statistically significant, actually the difference between the two groups does not appear to be of importance.

The threatened loss of a position carrying with it considerable cumulative value, such as pension rights, etc., is a deterrent to relapse as suggested by the high percentage of success among civil service employees. The same is true of employees who have been promoted to positions of trust and authority. Of 42 patients with on the job authority of "foreman," 71.4 per cent remained abstinent; 55 per cent of 647 patients with the title of manager remained abstinent. The records of 1204 patients who had no authority whatsoever showed that only 43.7 per cent remained abstinent. For some reason, not apparent, only six of 18 patients with the rank of superintendent remained abstinent.

The work record of an individual appears to be a quite sensitive indicator of his chances of remaining abstinent following treatment. From table 5 it may be seen that those with a good record, as indicated by few changes of jobs and minimal unemployment, remained abstinent in 70.9 per cent of the cases. Those with a history of frequent unemployment and changes in jobs remained abstinent in only 21.1 per cent of the cases.

A similar trend is noted among patients owning and managing their own places of business. Those who accomplished this well remained sober in

62.2 per cent of the cases. Those who were frequently absent from their business or whose friends and relatives often found it necessary to render assistance remained abstinent in only 27.5 per cent of the cases.

Employees who were desirable workmen when sober but lost excessive time from work because of drinking were below average risks as only 40.8 per cent of these patients remained abstinent.

TABLE V

The Relation between the Patient's Work Record and the Percentage of Abstinence

Work Record	Cases in Group	% Abstinent
Good employee with few changes of employer	509	70.4
Poor employee, many changes of employer, frequently unemployed	332	21.1
Managed own business well by himself	98	62.2
Managed own business poorly, required help of others	178	27.5
Good worker when sober but much lost time from drinking	390	40.8

*The Patient Who Owns His Own Business.* It is of interest that patients who owned their business remained abstinent in 50.4 per cent of the cases while business men who operated a business for others remained abstinent in only 46.8 per cent (table 4). Further analysis of this factor for the group when farmers, retired and professional men are excluded revealed that 47.7 per cent of those owning their own business entirely remained abstinent; those owning but a part of a business enterprise remained abstinent in 43.7 per cent of the cases; 45.4 per cent of those having no financial interest in their occupation remained abstinent. From this viewpoint the fact that a patient owns his business is not so important as how well he manages it.

TABLE VI

Relation between the Financial Status and Percentage of Abstinence

Financial Status	Cases in Group	% Abstinent
Indigent	334	20.0
Middle class	1619	49.4
Wealthy	116	62.1

*The Financial Status of the Patient.* Table 6 reveals a direct correlation between the financial status of the patient and his chances of remaining abstinent following treatment. Only 20.0 per cent of 334 patients classified as indigent remained abstinent; 49.4 per cent of 1619 middle class patients remained abstinent; 62.1 per cent of 116 patients considered to be wealthy remained abstinent. A few very wealthy patients were treated but their numbers were insufficient to be considered statistically.

*Payment of the Treatment Fee.* Table 7 reveals even greater correlation between the percentage of abstinence and the method of financing the cost of treatment. Of 73 patients who were given treatment without charge



TABLE VII

Relation of Ability to Pay for Treatment and the Percentage of Abstinence

Person Paying for Treatment	Cases in Group	% Abstinent
Charity case, no charge made	73	9.6
Paid by friends or relatives	223	25.1
Patient paid fee from own funds	1832	48.6

only 9.6 per cent remained abstinent; 25.1 per cent of 223 patients whose treatment fee was paid by friends or relatives remained abstinent; 48.6 per cent of 1823 patients paying the treatment fee from their own funds remained abstinent. The disappointing results with charity patients is surprising for individuals before being considered eligible for free treatment were investigated thoroughly and found to be exceptionally worthwhile persons. This figure suggests that conditioning therapy might not be efficacious when given in free clinics.

*Distance the Patient Comes to Receive Treatment.* This factor was analyzed as shown in table 8. Patients residing within the County in which the sanitarium is located remained abstinent in 41.9 per cent of 903 cases; 45.0 per cent of 775 patients living outside King County, but within a radius of 100 miles remained abstinent; 47.9 per cent of 334 patients living between 100 and 500 miles from the sanitarium remained abstinent; 50.4 per cent of 111 patients traveling 500 to 1000 miles to receive treatment remained abstinent; 54.5 per cent of 22 patients living more than 1000 miles away remained abstinent. These data offer evidence that the percentage of successful results following conditioning therapy increases proportionately to the distance the patient must travel to receive treatment. The beneficial factor of affluence is also probably present in those traveling the longer distance although its exact rôle cannot be determined from the data available. Patients arriving from foreign lands to receive treatment were too few to warrant statistical consideration.

TABLE VIII

Relation of the Distance Patient Must Travel to Receive Treatment and Percentage of Abstinence

Distance Traveled	Cases in Group	% Abstinent
Residing within King County	903	41.9
Residing outside county but within 100 miles	775	45.0
Residing from 100 to 500 miles distant	334	47.9
Residing from 500 to 1000 miles distant	111	50.4
Residing from 1000 to 2000 miles distant	22	54.5

*The Patient's Place of Residence.* Since community life varies widely between that found in urban centers and towns, villages and farms it was thought wise to investigate this factor. Table 9 shows what appears to be a significant correlation. Of 1173 patients residing in a city, 40.8 per cent remained abstinent; 43.6 per cent of 848 patients living in a town remained

TABLE IX

Relation between Place of Residence and Percentage of Abstinence

Residence	Cases in Group	% Abstinent
City (over 100,000 pop.)	1173	40.8
Town (under 100,000 pop.)	848	43.6
Village (1000 pop. or under)	61	65.6
Farm	101	56.4

abstinent; 56.4 per cent of 101 patients residing on a farm remained abstinent; 65.6 per cent of 61 patients living in a village remained abstinent. It would seem that the least favorable place of residence is within a city while the optimum residential location is in a village. These data do not correspond exactly to those given in table 4 as in some instances patients whose occupation is farming, nevertheless, live in a village or town while some living on a farm do not follow this vocation in making a living.

*The Patient with a Police Record.* Two hundred fifty of our patients had been arrested and convicted of one of the following charges: Passing worthless checks, disorderly person, habitual drunkenness, revocation of driver's license for drunken driving, larceny, embezzlement, moral charges and for unknown reasons. Only 21.6 per cent of these 250 patients remained abstinent following treatment.

*The Nervous Patient.* On admission 898 patients considered themselves to be inherently "nervous." Only 32.7 per cent of this group of patients remained abstinent, a figure significantly below the average for the entire series.

*The Patient Who Has Suffered a Nervous Breakdown.* Twenty-one patients gave a history of having suffered a nervous breakdown at some time in the past. Of this group, a single patient had remained abstinent at the time the survey was made. It would thus appear that conditioning therapy alone has little to offer this type of patient although it should serve as a valuable adjunct to other forms of treatment.

*The Patient with a Physical Deformity.* Forty-five patients were noted as having a physical deformity upon admission. These deformities included loss of a limb, paralysis, total alopecia, disfiguring acne, loss of an eye and congenital deformities. Eighteen of these patients or 40.0 per cent remained abstinent. While such a physical handicap appears to militate against a successful result to some degree, it is surprising that this group on the whole did so well.

*The Periodic Versus the Steady Drinker.* Surprisingly few of our patients were true periodic alcoholics. This was possibly due, in part, to many of the records concerning the patients' drinking habits being incomplete or ambiguous in this respect. In order to be classed as a true periodic drinker it was necessary that the patient indulge in prolonged sprees with an equal or greater period of abstinence between. Only 24 such patients were found. Fourteen or 58.3 per cent were abstinent at the end of

1945. Of 449 patients treated during the same period whose history allowed them to be definitely classified as steady drinkers, only 206 or 45.8 per cent had remained abstinent. While it is dangerous to attach too great significance to these figures because of the imbalance in size between the two groups, the results are nevertheless surprising for it is generally believed that the periodic alcoholic represents the true psychopathologic alcoholic, yet in this instance the greatest benefit accrues in this group as a result of therapy which supposedly carried with it no element of psychotherapy.

*The Patient with an Enlarged Liver.* Physical examination records show the liver was palpable in 402 patients on admission. The percentage of abstinence in the group with enlarged liver was 52.9 per cent; among 1567 patients who did not have an enlarged liver the rate of abstention was 43.6 per cent. These figures suggest the concrete evidence thus furnished that alcohol consumption has been harmful to the patient serves as a definite deterrent to relapse.

*The Patient Who Has Had Delirium Tremens.* The record shows that 210 patients had suffered from delirium tremens prior to admission or had an episode of delirium during the disintoxication period in this institution. The rate of abstinence among those who had suffered delirium tremens was 34.3 per cent; among 1737 patients who had escaped delirium the abstinence rate was 46.2 per cent. These data suggest that delirium tremens may be not only a manifestation of acute toxemia but also an early symptom of alcoholic deterioration. Certainly the chance of remaining abstinent following delirium tremens is markedly impaired.

*The Number of Years a Patient Drank before Seeking Treatment.* Of 93 patients who had drunk for a period of less than five years, 32.2 per cent remained abstinent; 44.5 per cent of 276 patients who had drunk from six to 11 years remained abstinent; 48.1 per cent of 293 patients who had drunk from 11 to 15 years remained abstinent; 55.5 per cent of 362 patients who had drunk from 16 to 20 years remained abstinent; 53.1 per cent of 177 patients who had drunk from 21 to 25 years remained abstinent; 57.7 per cent of 225 patients who had drunk for 26 years or more remained abstinent.

It would be natural to question immediately whether this were not a false conclusion resulting from the presumption that the patients who had drunk the longest were older and therefore would fall into the more favorable age group so far as abstinence was concerned as shown in table 2. That such is not the fact is indicated by the average age of each group as shown in table 10. In the group of patients who had drunk less than five years the average age was found to be 38.6 years. On the basis of age alone an abstinence rate of 42.5 per cent should be expected for this group (table 2). Also, the average age does not vary significantly between this group and the next two, those drinking from six to 10 and 11 to 15 years respectively, yet the abstinence rate in the latter two groups is 44.5 per cent and 48.1 per cent.

TABLE X

Relation between Length of Time Patient Drank and the Percentage of Abstinence

Years Patient Drank	Cases in Group	Avg. Age	% Abstinent
Less than 5	93	38.6 yrs.	32.2
6 to 10	276	38.1	44.5
11 to 15	293	38.1	48.1
16 to 20	362	42.1	55.5
21 to 25	177	45.8	53.1
26 or more	225	52.7	57.7

On the basis of the data presented it appears that the longer a patient drinks before seeking assistance the better are his chances of remaining abstinent following therapy.

*The Patient Who Had Remained Abstinent Prior to Treatment.* A great many of our patients had remained voluntarily abstinent prior to admission. In most instances the period of abstinence had been inconsequential, lasting from two weeks to a month. In 82 cases, however, the period of abstinence had ranged from one to eight years. It was found that 54.9 per cent of these 82 patients remained abstinent following treatment, a rate significantly higher than that for the entire series.

It is probable that these patients possessed better insight into the necessity of remaining entirely abstinent following treatment for they had already demonstrated to themselves their inability to again drink normally following extensive periods of sobriety.

*Patients Referred by Physicians.* Our patients are about equally divided between those brought to the institution by friends or former patients and those referred by physicians. Abstinence among patients referred by a physician was found to be 43.4 per cent while among those not consulting a physician before admission the rate was 50.0 per cent. This fact may possibly be explained by the observation that, in general, the more severe types of alcoholics are apt to seek consultation with their family physicians prior to admission to an institution.

*The Type of Liquor Habitually Consumed.* Table 11 shows a slightly significant relation when the type of liquor habitually consumed is correlated with the percentage of abstinence following treatment. Whiskey drinking is most likely to be followed by sobriety for 45.9 per cent of 1262 patients who had been addicted to this liquor remained abstinent; 41.2 per cent of

TABLE XI

Relation between Type of Liquor Habitually Consumed and the Percentage of Abstinence

Type of Liquor	Cases in Group	% Abstinent
Gin	20	15.5
Wine	227	40.1
Beer	347	41.2
Whiskey	1262	45.9

347 patients who drank little but beer remained abstinent; and 40.1 per cent of 227 wine drinkers remained abstinent. Only 15.5 per cent of 20 patients habituated to gin remained sober but the total number of such patients is too small to attach great significance to this figure.

*The Rôle of Group Lectures by a Physician.* During a period of military duty while stationed in Seattle, one of us made it a practice to visit the sanitarium periodically to give lectures to groups of patients who had finished treatment. These talks attempted to explain the nature of alcoholism, the necessity for complete and permanent abstinence, the many pitfalls to be encountered, the necessity for reinforcement and other matters designed to further the alcoholic's understanding of his situation. A total of 253 patients attended these lectures and at the time the survey was closed it was found that 157 or 62 per cent were still abstinent. A group of 253 patients treated during the same period who were prevented from attending the lectures for various reasons were examined and it was found that 151 or 59.6 per cent had remained abstinent. Apparently the simple expedient of group lectures plays little or no rôle in maintaining abstinence.

*Method of Liquor Sale Control in the Patient's Home State.* If the patients from Washington are excluded it is found that the out of state patients are divided numerically into two approximately equal groups; one group resided in states which have (or had at the time of this survey) a system of state control of liquor sales which allowed free sale of beer and wine but restricted the sale of distilled spirits to certain state supervised liquor stores. The other group came from states allowing the unrestricted sale of liquor of all types in cocktail bars, taverns, etc. When a comparison of the relative rate of abstinence following treatment for the two groups is made it is found that the patients residing in states with government control of liquor sales remained abstinent in 40.4 per cent of the cases while those living in states allowing the unrestricted sale of all types of liquor showed an abstinence rate of 45.2 per cent.

It would thus appear that attempted control of liquor sales by government agencies certainly does not enhance the chances of sobriety following treatment. Since the states with government control are grouped around Washington the factor of distance was carefully considered and found to be insignificant in affecting these data.

*Interest in Abstinence Clubs.* Abstinence clubs have been formed by patients in almost every community in which a sufficient number of eligible individuals reside. These clubs have various names and are not connected with the sanitarium except that all members have received conditioning therapy. The remarkable salutary effect of these organizations may be adduced from the fact that abstinence among the members was 87.4 per cent. Among a group of similar size, the members of which expressed an antipathy to such group activity, the abstinence rate was 40.4 per cent.

The great majority of our patients find little of interest in the local Alcoholics Anonymous group. We have been successful with some indi-

viduals who have not been helped by the latter organization and the converse is also true. In general, however, the two groups of patients are not miscible. It is not logical to presume that each group possesses a peculiar psychological homogeneity. We believe the absence of a communal spirit between the two groups to be merely another expression of Fleming's observation that "practically every form of therapeutic approach has been successful—all have their coterie of enthusiastic advocates, all are fanatically intolerant of any approach but their own—."

*Military Service.* Forty-four of our patients enlisted or were inducted into the service during the war. Seventeen or 38.6 per cent were still abstinent when discharged. Considering the many psychological pitfalls encountered during military service it is surprising that this small group was able to establish such a fine record of sobriety.

*The Coöperative Patient.* Since 1940 patients have been given the opportunity of periodic return for reinforcement. The celerity with which a patient avails himself of this adjuvant to success is a measure of his sincerity and coöperation. Most patients coöperated well with the reinforcement program during the early months following initial treatment but only 194 were found to have complied faithfully with all the requirements of the reinforcement schedule that had been set up for them for the entire year. When this group of ultra-coöperative patients was examined it was found that 86.1 per cent of the cases remained abstinent. This is a remarkable record for it should be recognized that none of the patients treated during 1945 could be included in the group. It had not been determined at the time the survey was closed at the end of 1945 whether those treated during that year would or would not coöperate during the ensuing 12 months. Thus, the statistical advantage of including the high abstinence group of recently treated patients was lost.

#### CAUSES FOR RELAPSE

Six hundred ninety-three patients who relapsed did not appear at the sanitarium subsequently; the alleged reason for their relapse is consequently unknown. Table 12 lists the reasons given for relapse among 496 cases in whom definite information is available. The data are divided into two parts: first, the cases relapsing for reasons which indicate that failure might have been averted had adjuvant psychotherapy been administered, and second, those relapsing for causes that probably would have been uninfluenced by psychotherapy.

The first group consists of 284 patients whose reasons for relapse were as follows: because of mental depression 122; because of overwork, nervousness or insomnia 44; because of boredom 11; because of continued association with drinking companions 51; following a quarrel 38; worry over health 18. If the same ratio may be presumed to have existed among the group of unknown relapses it may be postulated that 677 patients or about 30 per

TABLE XII  
The Alleged Reason for Relapse in 496 Cases

Reason for Relapse	Cases in Group
A. <i>Relapse might have been prevented by psychotherapy</i>	
Mental depression	122
Overwork, nervousness, insomnia	44
Boredom	11
Continued association with drinking companions	51
Following a quarrel	38
Worry over health	18
B. <i>Relapse probably not preventable by psychotherapy</i>	
Continued drinking by spouse	17
Believed selves able to drink normally	85
Ashamed to admit they could not drink	11
Curiosity as to effect a drink would have	33
Took alcohol by mistake	10
Treated under duress, later deliberate relapse	39
Craving not eliminated by conditioning	12

cent of the cases comprising the entire series probably should have received psychotherapy in addition to conditioning procedures. This figure supports our previous statement that conditioning therapy alone appears to be adequate treatment in about 70 per cent of all alcoholics.

The reasons for relapse in the second group are listed as follows: Because of continued drinking by spouse 17; because they still believed themselves able to drink in a normal manner 85; because they were ashamed to admit they could not drink 11; because of curiosity as to what would happen if a drink were taken 33; because a drink was ingested by mistake 10; because treatment was accepted under duress with subsequent deliberate relapse 39; because of no apparent reason 5; and, because of continued craving for liquor 12. It is reasonable to suppose that psychotherapy would have been of little value in preventing these relapses for the danger manifest in the above situations had been thoroughly explained to each patient upon discharge.

*The Period of Abstinence Enjoyed by Those Who Relapse.* The record is sufficiently accurate in 868 unsuccessful cases so that the period of abstinence enjoyed prior to relapse may be tabulated. From table 13 it may be seen that 97 patients remained abstinent less than one month fol-

TABLE XIII  
The Period of Abstinence Enjoyed by 868 Patients Who Relapsed

Months Abstinence after Treatment	Cases in Group
Less than 1 month	97
1 month	54
2 months	74
3 to 6 months	228
7 to 12 months	139
13 to 18 months	84
19 to 24 months	72
25 to 30 months	26
31 to 36 months	19
36 months or over	75

lowing treatment; 228 remained abstinent from three to six months; 139 remained abstinent from seven months to one year; 156 remained abstinent from 13 months to two years; 45 remained abstinent from 25 months to three years; and 75 remained abstinent for 36 months or longer. When calculated on an average basis this figure becomes 11.2 months for each patient. Thus it may be said that even in those patients who relapsed the results of therapy were well worth while.

It is also interesting to calculate what this period of sobriety means to industry, or to the war effort during the time covered by the survey for it is equivalent to an army of 9,721 men working steadily for a period of 30 days.

#### AN ATTEMPT TO SELECT PATIENTS IN RETROSPECT

While several specific factors have been shown to exert a profound effect upon the patient's ability to remain abstinent, further examination of the data shows that the factors considered are not the only ones involved or in fact, are probably even not the most important. Upon attempting to select the patients in retrospect on the basis of what is presently known from the preceding data it was found that had all applicants who were characterized by one or more of the unfavorable factors refused treatment, the number of relapses would have been reduced from 1281 to 673, indicating an increase in the average abstinence figure from 44.8 per cent to 55.5 per cent. However, this method of selection would have prevented a total of 809 patients from receiving treatment and thus would have been an illogical basis for rejection of the 201 supposedly unsuitable patients who, nevertheless, remained abstinent; nor would such criteria have been successful in screening out 608 patients who would have been considered suitable candidates for conditioning therapy yet subsequently relapsed. Obviously insufficient information is available at this time to make possible accurate selection of patients for conditioning therapy alone. The material presented is a step in the right direction, however, and even now might prove of value in the prescription of adjuvant therapy. The need for further research along these lines is apparent.

#### DISCUSSION

The series of alcoholic patients here reported, treated by conditioned reflex therapy alone, or in conjunction with varying amounts of social service and field rehabilitation, represents so far as is known one of the largest series of cases reported from a single source in this country. Statistical analysis of known cases proves, beyond argument, that conditioning therapy, when properly executed, is one of the most efficacious and probably the most economical of methods for treating chronic alcoholism available at this time. When considering those patients who relapsed, the short time and small expense involved in the conditioning procedure has been shown to be well spent for even these patients had enjoyed a not inconsiderable



period of abstinence prior to relapse. It is hoped that the most gratifying results herein reported will encourage others to master the technic and utilize it in the treatment of chronic alcoholics elsewhere. Certainly the method has been observed sufficiently long with statistical consideration of a large enough series of cases to convince the most skeptical of its inherent value.

It is difficult to compare the value of conditioning methods with others for the simple reason that statistical data in the latter are extremely rare. Such statements as that attributed to the Alcoholics Anonymous group that "70 per cent of our members are benefited" are valueless not only because of failure to consider the time element but also because this statement could mean almost anything depending upon the interpretation of the word "benefited." Furthermore, the statement is admittedly not based on a comprehensive statistical survey of all or even a relative segment of the members. Many other authors report their results in ambiguous terms without establishing a definite criterion for a successful result or by neglecting the important length of abstinence factor altogether. Proper evaluation of the various technics must await accurate statistical reporting of their results. A plea for such is hereby made.

Since the data concerning the factors likely to affect prognosis were collected from a series of patients treated by conditioning methods alone it cannot be definitely stated that the conclusions drawn from this portion of the study would apply equally to cases of chronic alcoholism treated by other methods. Such factors as age, marital state, family discord, occupation, the financial status, place of residence, conflict with the law, nervousness, physical deformity, history of delirium tremens, the length of the drinking history and record of prior abstinence all appear to exert a specific effect on the eventual outcome of the patient. These factors may be evaluated upon admission and should help indicate the need for adjuvant psychotherapy or other methods of treatment. Unfortunately, the subsequent coöperativeness of the patient and his interest in group abstinence clubs cannot be determined except by inference prior to treatment.

Study of the cases relapsing following conditioning therapy suggests the probable need for psychotherapeutic methods of some sort in about 30 per cent of all alcoholics. This implies the desirability of diagnostic appraisal or evaluation before wholly effective therapy may be prescribed. It is in this field that our greatest inadequacy exists. No magic formula has yet been found capable of reducing the complexities of the patient's personality to a figure that indicates whether conditioning therapy alone will suffice or if adjuvant technics are necessary. It is believed that the data reported at this time will assist somewhat and it is hoped that current research directed toward minute investigation of various physical, physiological and psychiatric factors may, in time, yield the key to unlock the mysteries of the patient's personality so that comprehensive therapy, without redundancy, may be formulated after a short period of study.

While the value of conditioning therapy has been shown not only by ourselves but by others,<sup>6,7</sup> the value of formal psychotherapy, psychological technics, social service activities, physical rejuvenation and other modes of treatment in conjunction with conditioning has, as yet, not been proved. It is possible that they will not enhance sensibly the results that are obtained by conditioning alone. The war years prevented much of our research planned for the early years of this decade. It was not until 1946 that the preliminary report of our first attempt to incorporate one phase of psychotherapy, pentothal interview, with conditioning was made.<sup>8</sup> The results were encouraging but not conclusive since the experimental group was small (35 cases) and the period of observation rather brief (8 to 18 months). Since the closing date of this survey, late in 1945, nearly 2000 additional patients have been treated. The latter group received varying amounts of psychotherapy, intensive physical rejuvenation, more comprehensive social service and field rehabilitation and in many cases, pentothal interview. Investigation and analysis of these patients will doubtless yield valuable information concerning the value and indications for these adjuvant methods of treatment. When this has been accomplished, either by ourselves or others working along similar lines, a tremendous forward step will have been made, for familiarity with all available technics and the ability to prescribe them intelligently should be the goal toward which all therapists should strive. It is high time that we cease being "fanatically intolerant of any approach but (our) own."

#### SUMMARY AND CONCLUSIONS

Data concerning 3125 admissions to this institution during the ten and a half years ending with 1945 have been collected and analyzed. A net series of 2323 cases treated by the conditioned reflex method has been subjected to statistical evaluation. As a result the following conclusions appear to be warranted:

1. Conditioning procedures, when used alone, will cause 85 per cent of all chronic alcoholic patients to remain abstinent for six months or longer; 70 per cent will remain abstinent for one year or longer; 60 per cent will remain abstinent for two years or longer; 55 per cent will remain abstinent three years or longer; 40 per cent will remain abstinent four years or longer; over 30 per cent will remain abstinent for seven years or longer; and about 25 per cent will remain abstinent ten and a half years or longer.

2. The factors of age, marital state, family discord, occupation, financial status, place of residence, conflict with the law, nervousness, physical deformity, delirium tremens, length of drinking history and record of prior abstinence have been shown to affect the prognosis either favorably or unfavorably. It is suggested that evaluation of these factors would be of benefit in formulating treatment. Interest in abstinence clubs and a high degree of coöperativeness by the patient are also of great value in achieving success.

3. Patients who relapse following conditioning therapy enjoy on an average 11.2 months of sobriety between treatment and the time they resume drinking. Thus even in those who fail, therapy has been socially and economically of value.

4. The inherent value of conditioning therapy has been proved beyond question by these data. It is believed that adjuvant methods, such as psychotherapy, social service and rehabilitation, physical rejuvenation, etc., should enhance the results when they are combined with conditioning methods, but this, as yet, has not been proved.

5. The struggle against the encroachments of chronic alcoholism requires the use of every weapon of proved value. Conditioning technics should be thoroughly mastered and incorporated into existing therapeutic plans throughout the country as an important research yet to be done. Singularity of therapeutic purpose is admirable but stubborn singularity of method is to be condemned when it stands in the way of research and progress. The results of treatment by any method should be clearly defined and analyzed statistically to allow impartial evaluation and comparison with others.

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# LIVER FUNCTION AND SERUM PROTEIN STRUCTURE IN GOUT \*

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THE medical literature of the past century contains numerous references to the supposed rôle of the liver in gout.<sup>7 through 15, 23, 24, 30, 31, 42, 50, 55, 62, 63, 79</sup> Three types of hypothesis have been presented: (1) that gout results from an isolated disturbance in some hepatic enzyme, (2) that gout results from chronic diffuse hepatic impairment, and (3) that hepatic impairment is a frequent visceral complication of gout. The first hypothesis is as yet difficult to evaluate, since suitable methods of study have only recently become available.<sup>31, 32, 33</sup> The latter two hypotheses may be evaluated by means of the known sensitive liver function tests.

The present study was undertaken to determine the frequency and pattern of abnormal hepatic function in gout. A detailed study of serum protein partition was carried out to check those tests which depend primarily upon serum globulin structure and to aid in comparing changes in gout with those reported in rheumatoid arthritis.

## SUBJECTS

Forty-three patients studied were classified in four groups: (1) interval gout, (2) acute and subacute gouty arthritis, (3) chronic gouty arthritis, and (4) gout with known complicating disease. A patient with an acute exacerbation of a chronic gouty arthritis was considered to be in Group 2. The fourth group included only those patients whose complicating disease was of such a nature that it might be expected ordinarily to lead to hepatic involvement. Group 4 included two patients with chronic hepatitis presumably due to alcohol, one with chronic congestive heart failure, one with long-standing chronic ulcerative colitis, one with chronic hepatitis following infectious hepatitis, and one with idiopathic lipemia. Three patients studied both during an acute episode and during remission appear in two groups.

## RESULTS

*General Pattern of Liver Function.* Table 1 lists the number of determinations of each variety performed and the number of abnormal results. Table 2 gives average values for the results of those tests which yield a quantitative

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TABLE I

## Liver Function Tests in Patients with Gout

(The numerators in the table indicate the number of abnormal results obtained; the denominators indicate the number of tests performed. Where percentage values are given, they refer to the percentage of abnormal results. Three patients appear in each of two categories.)

	Interval Gout	Acute and Subacute Gouty Arthritis	Chronic Gouty Arthritis	Gout with Known Complicating Disease	All Gout Patients
Number of patients	17	16	7	6	43
Serum bilirubin	0/11	0/10	0/11	0/ 6	0/38 ( 0.0%)*
Total protein	1/18	2/15	3/15	2/10	8/58 (13.8%)*
A/G ratio	0/18	0/15	1/15	3/10	4/58 ( 6.9%)
Total cholesterol	0/14	0/14	1/14	7/13	8/55 (14.5%)
% Cholesterol ester	0/11	1/10	1/11	3/ 9	5/41 (12.2%)
Thymol turbidity	2/13	3/12	4/13	9/10	18/48 (37.6%)
Thymol floc.	0/12	1/12	0/13	0/10	1/47 ( 2.1%)
Cephalin floc.	0/11	3/11	4/10	3/ 7	10/39 (25.6%)
Colloidal gold floc.	0/ 7	2/ 8	0/ 2	—	2/17 (11.8%)
B.S.P. and alkaline phosphatase	0/ 3	1/ 4	0/ 3	2/ 3	3/13 (23.1%)
All tests	3/118 (2.5%)	13/111 (11.7%)	14/107 (13.1%)	29/78 (37.2%)	59/414 (14.3%)

\* No low values were found; the eight abnormal results all represent serum protein values greater than 8.0 gm. per cent.

TABLE II

## Mean Values for Liver Function Tests Giving Quantitative Results in Patients with Gout

(Numbers in parentheses are the number of tests performed. Values for the thymol turbidity test results are median values, rather than averages. "Albumin" and "globulin" values are those determined by the Howe method.)

Total Protein, gm. %	"Albumin," gm. %	"Globulin," gm. %	A/G Ratio	Total Cholesterol, mg. %	Per Cent Esters	Thymol Turbidity, units	Bilirubin, mg. %
Interval gout							
7.39 (18)	5.30 (18)	2.09 (18)	2.53 (18)	221 (14)	71 (11)	2.1 (12)	0.6 (11)
Acute and subacute gouty arthritis							
7.20 (14)	5.00 (14)	2.20 (14)	2.27 (14)	162 (14)	68 (10)	2.2 (12)	0.4 (10)
Chronic gouty arthritis							
7.26 (15)	4.93 (15)	2.33 (15)	2.12 (15)	199 (14)	70 (11)	2.1 (13)	0.5 (11)
Gout with known complicating disease							
7.48 (10)	4.78 (10)	2.70 (10)	1.77 (10)	259 (13)	67 ( 9)	3.6 (10)	0.5 ( 6)

result. Abnormal findings were rare in uncomplicated interval gout (2.5 per cent). They were somewhat more common in acute gouty arthritis (11.7 per cent) and chronic gouty arthritis (13.1 per cent). This suggested that the abnormalities might be related to the activity of the articular involvement. Nevertheless, in neither of the latter two groups did the number of abnormal findings approach that seen in the patients with gout and known complicating disease (37.2 per cent).

*Group A and Group B Tests.* By dividing the test battery into two groups, it could be shown that the increased percentage of abnormal results noted during acute and chronic gouty arthritis showed a pattern which was qualitatively different from that found in gout patients with known complicating disease.

*Group A* includes tests which depend primarily on serum protein structure: serum total protein, A/G ratio (Howe method), thymol turbidity, thymol flocculation, cephalin flocculation, and colloidal gold flocculation. Since the serum globulins appear to be produced by the entire reticulo-endothelial system and not by the liver alone,<sup>1, 2</sup> these tests may not reflect liver function alone.

*Group B* includes tests which do not depend primarily on changes in serum proteins: serum bilirubin concentration, serum total cholesterol, cholesterol partition, bromsulfalein excretion, and alkaline phosphatase.

TABLE III

## Analysis of Abnormalities in Liver Function Tests Found in Gout Patients

(The basis for division of the test battery into Group A and Group B, and the composition of the two groups of tests, are given in the text. In the table, numerators represent the number of abnormal results obtained, denominators are the number of tests performed. The values in parentheses are the percentage of abnormal results.)

	Group A Tests	Group B Tests	All Tests
Interval gout	3/ 79 ( 3.8%)	0/39 ( 0.0%)	3/118 ( 2.5%)
Active gouty arthritis (Acute, subacute, and chronic)	23/139 (16.5%)	4/79 ( 5.1%)	27/218 (12.4%)
Gout with known complicating disease	17/ 47 (36.2%)	12/31 (38.7%)	29/ 78 (37.2%)

Table 3 summarizes results obtained by dividing the tests in this manner. In patients with known complicating disease, abnormalities in Group A tests (36.2 per cent) occurred with about the same frequency as abnormalities in Group B tests (38.7 per cent). On the other hand, during active gouty arthritis (acute, subacute or chronic) abnormalities in Group A tests (16.5 per cent) occurred more than three times as frequently as abnormalities in Group B tests (5.1 per cent). The few abnormal results found in patients with interval gout fell entirely into Group A. It thus appeared that abnormal test results found in active gouty arthritis were chiefly referable to tests

which depended upon serum protein structure. Moreover, the abnormalities found in gout patients with known complicating disease (37.2 per cent) far exceeded the number found in all of the other gout patients (8.9 per cent); so much so as to suggest that when alterations were found in members of the latter group, they result chiefly from conditions other than gout.

*Serum Proteins.* Average serum total protein values for the various groups (table 2) ranged from 7.20 to 7.48 gm. per cent, a high normal range of values for ambulatory adults. No patient had a total protein below 6.2 gm. per cent; but values above 8.0 gm. per cent were noted in 8 of 58 determinations.

The Howe sodium sulfate method gave average serum "albumin" \* values which varied from 4.78 gm. per cent to 5.30 gm. per cent in the different groups (table 2). These normal findings do not confirm Ficarra's belief that hyperuricemia is associated with hypoproteinemia or hypoalbuminemia<sup>3,4</sup> but serve rather to illustrate the excellent nutritional state of the general run of gout patients. The A/G ratios (Howe method) averaged well above the minimum normal value of 1.38 in all of the groups of patients. The lowest average serum "albumin" value (4.78 gm. per cent), the highest average serum "globulin" value (2.70 gm. per cent), and the lowest average A/G ratio (1.77) occurred in the patients with known complicating disease. None of these findings are notably abnormal.

Table 4 gives average results of serum protein studies obtained by the use of a chemical procedure which gives results comparable to those of electrophoretic analysis.<sup>5,6</sup> The average values for the entire group of patients do not differ significantly from normal values, except perhaps in a minimal elevation of the beta-globulin content. Further analysis of the material shows that the patients who are free of significant hepatic or renal impairment show no abnormalities in serum protein partition. Patients known to have hepatic impairment had a diminished A/G ratio, and elevations in beta-globulin and gamma-globulin. Patients with significant renal impairment (defined as glomerular filtration rate below 60 c.c./min./1.73 sq. m.) had significant increases in all three globulin fractions, as well as a diminution in the true A/G ratio.

On the whole, serum protein structure appeared generally normal in gout. The total protein concentration was never low, and occasionally was somewhat elevated. When marked visceral impairment was absent, the fractionation pattern appeared normal. When visceral impairment was present, the changes found were only moderate. The results of qualitative liver function tests which depend on globulin structure suggest that some changes may occur in acute and chronic gouty arthritis; but these are found only in

\* The "albumin" values given by the Howe method include both albumin and alpha-globulin, as estimated by electrophoretic analysis or by chemical technic standardized against electrophoresis.<sup>5,6</sup> The term *true A/G ratio* used elsewhere in this article denotes the ratio as calculated from electrophoretic data or from data obtained by a chemical method standardized against electrophoresis.

TABLE IV

## Distribution of Serum Protein Fractions in Gout

(Serum protein fractionations were performed by the chemical method of Cohn and Wolfson.<sup>5,6</sup> The normal values quoted are those obtained by repeated analysis on four samples of pooled serum from professional donors, each pool being derived from between 30 and 150 individuals. Chemical analyses of two of these pooled serums were checked against electrophoretic runs.)

Group of Patients	Number of Patients	Serum Total Protein, gm. %	Albu- min, gm. %	alpha glob., gm. %	beta glob., gm. %	gamma glob., gm. %	A/G Ratio	Albu- min, % TP	alpha glob., % TP	beta glob., % TP	gamma glob., % TP
Normal adults											
Average Normal		7.01	3.77	1.10	0.94	1.20	1.16	54%	16%	13%	17%
Gout patients											
No hepatic or renal impairment	10	7.34	4.43	0.96	0.99	0.96	1.52	60%	13%	14%	13%
Hepatic impairment	5	7.62	3.48	1.28	1.40	1.46	0.84	46%	17%	18%	19%
Renal impairment	6	7.12	3.27	1.42	1.18	1.25	0.85	46%	20%	16%	18%
All gout patients.....	21	7.34	3.87	1.17	1.14	1.16	1.12	53%	16%	16%	16%

a minority of such patients. These findings contrast markedly with those in rheumatoid arthritis, a distinction discussed more fully below.

*Serum Cholesterol.* A number of earlier writers<sup>7 through 15</sup> stated that elevated values for serum total cholesterol were frequent in gout. Determinations in our series were carried out by the Schoenheimer-Sperry technic<sup>16</sup> for which the normal range of serum total cholesterol is 120 mg. per cent to 300 mg. per cent. Mean values for the various groups of patients (table 2) were lowest during acute gouty arthritis (162 mg. per cent) and highest in the group of patients with known complications (259 mg. per cent). This latter value, however, is appreciably elevated by the inclusion of one patient with idiopathic lipemia and gout.\* With this patient excluded, the group average falls to 229 mg. per cent, but remains the highest of all of the groups of patients. These data indicate, that in spite of the frequency of renal impairment in gout, hypercholesterolemia is not common. The older reports appear to have been based on small average deviations, and the authors did not have the advantage of our present knowledge of the wide normal range of serum cholesterol values.

Deviation of cholesterol esters from the normal range of 65 per cent to 75 per cent of the total cholesterol was unusual. In only one instance, that of a patient with chronic hepatitis following infectious hepatitis, was a cholesterol ester below 60 per cent noted; four other determinations of the 41 performed, gave ester values between 60 per cent and 65 per cent of the total cholesterol.

*Serum Bilirubin.* No abnormal values were noted. All of 38 deter-

\* Complete clinical and laboratory data on this patient will be given in a forthcoming case report.



minations gave values of 1.0 mg. per cent or less, well below the upper normal value of 1.2 to 1.4 mg. per cent. The average values in the four groups of patients fell between 0.4 mg. per cent and 0.7 mg. per cent. This finding not only rules out any possibility of liver involvement of the intrahepatic obstructive variety in gout, but also suggests that if diffuse liver damage of any kind occurs regularly in gout, it must be very mild in degree.

## DISCUSSION

*Gout and the Liver.* The data derived from sensitive liver function tests suggest that hepatic involvement in gout is unusual. Abnormal results were obtained chiefly when a complicating disease known to impair liver function was present. However, some abnormal results were obtained in patients with active gouty arthritis. The tests which gave abnormal results during active gouty arthritis were chiefly those which depended upon serum protein structure, particularly globulin structure. These tests reflect both liver function and the function of the entire reticulo-endothelial system. As the extrahepatic reticulo-endothelial system participates in the response to trauma,<sup>2, 19 through 22</sup> such abnormalities may not indicate liver damage. The rarity of abnormal results on tests which do not depend on the integrity of the extrahepatic reticulo-endothelial system in patients with active gouty arthritis (5.1 per cent) is in marked contrast to the abnormal results (38.7 per cent) found in patients with known complicating disease. These data suggest that the abnormalities found in active gouty arthritis may depend upon reticulo-endothelial irritation and not upon liver damage.\*

*Specific Enzyme Abnormality Theory.* Chrometzka<sup>23, 24</sup> has been the most recent proponent of the idea that gouty hyperuricemia results from a deficiency of uricolytic enzyme in human liver. Apart from his unverified claim that a breakdown product of urate can be isolated from human urine,<sup>23, 24</sup> there is no evidence that the human liver does destroy urate. Considerable evidence can be marshalled against this view; particularly the fact that uricase, found in all species known to degrade urate, is not found in man or in the anthropoid apes whose purine metabolism resembles that of man.<sup>25, 26</sup>

There is, on the contrary, evidence to suggest that in man the liver may be the site of urate production. In the most severe cases of liver disease,†

\* A similar, but more general conclusion, in regard to the interpretation of the sensitive flocculation tests was reached by Mann, Snell and Butt.<sup>22</sup> These investigators studied the thymol turbidity reaction in cirrhosis, infectious hepatitis, and in certain systemic disorders. Both from their own results, and from a review of the literature on flocculation reactions, they concluded that such reactions were not necessarily correlated with hepatocellular injury, but might more reasonably be attributed to a general phenomenon of reticulo-endothelial irritability. They particularly emphasized the frequency of normal flocculation reactions in late cirrhosis, an observation which has been confirmed several times.

† Very low blood urate values, like very low serum urea values, are not the usual finding in moderately severe liver disease. Moderate degrees of hepatocellular involvement have as their chief consequences an increase in urate clearance, with some fall in blood urate concentration, and an increase in the minute urinary excretion of urate.<sup>34 through 37</sup>

blood urate levels may be extremely low.<sup>27, 28</sup> Moreover, in man, xanthine oxidase, the enzyme now believed to be responsible for urate production, occurs only in the liver.<sup>29</sup> It has been suggested that hyperuricemia may result from the withdrawal of normal inhibitory influences on hepatic xanthine oxidase.<sup>30</sup> An unsuccessful attempt to inhibit xanthine oxidase in vivo has been reported.<sup>31</sup> It is interesting that both colchicine and salicylate have been reported to inhibit xanthine oxidase.<sup>32</sup> The finding of abnormally low serum oxypurine concentrations in gout patients is consistent with the hypothesis of diminished inhibition of hepatic xanthine oxidase.<sup>33</sup>

*Effect of Biliary Obstruction.* As a certain proportion of the daily excretion of urate (estimated at about one-sixth of the total under normal conditions) occurs via the biliary tract and intestine,<sup>38 through 41</sup> mild hyperuricemia could conceivably result from biliary obstruction, intrahepatic or extrahepatic. This enterogenous fraction, difficult to measure because intestinal bacteria break down urate rapidly, is increased in the presence of renal damage<sup>39</sup> and during cinchophen administration.<sup>40</sup> As noted above, the normal serum bilirubin levels in gout patients would seem to indicate that biliary obstruction can play no rôle in the production of gouty hyperuricemia.

*Reported Abnormalities of Hepatic Function and Structure in Gout.* The literature contains a number of speculations on this problem, but actual data are sparse. Robecchi and Pescarmona<sup>42</sup> reported frequent abnormalities but included several tests, such as glycine tolerance, which are of dubious significance. Brøchner-Mortensen<sup>43</sup> believed that complicating disease satisfactorily accounted for most of the abnormalities which he found. Less than one-third of his patients had elevated values of urine urobilinogen, even though his series of 24 patients included two with polycythemia vera and one with pernicious anemia. Five of 18 patients studied had increased values of serum quinine-resistant lipase<sup>44</sup>; but no abnormal galactose tolerance tests were found in 14 patients.

On the basis of clinical and laboratory findings, McCracken, Owen and Pratt<sup>45</sup> felt that a clinical diagnosis of hepatic cirrhosis was warranted in four of their 100 gout patients. All four of the patients were included in a group of 26 in whom the intake of alcohol was "frequent and excessive." Chrometzka<sup>24</sup> reported three abnormal galactose tolerance tests. Edgcombe<sup>50</sup> stated that the fructose tolerance was often abnormal. Ten oral glucose tolerance tests carried out by de Bonis<sup>51</sup> gave no clear evidence of hepatic impairment.

Steinberg and Lowenstein<sup>52</sup> reported normal Weltmann reactions in two patients with acute gouty arthritis. The Takata-Ara reaction was negative in all of seven patients studied by Miles and Salt.<sup>53</sup> The same authors reported a shortened Weltmann coagulation band (shift to the left) in three gout patients whose sedimentation rate was elevated, but not in four others whose sedimentation rate was normal. This is confirmed by Wuhrmann

and Wunderly, who also note that the changes are apt to be rather slight.<sup>53a</sup> Miles and Salt noted the *plasma* formol-gel reaction to be abnormal in the three gout patients whose sedimentation rate was elevated. Gibson and his co-workers,<sup>82, 83</sup> on the other hand, found the *serum* formol-gel reaction in gout frequently normal in spite of an elevated sedimentation rate. The distinction between the results of the formol-gel reaction on serum and on plasma has considerable theoretical significance and is discussed in further detail below. Coke<sup>54</sup> states that the thymol turbidity test is "often positive," which suggests an experience similar to ours.

Studies of gouty livers at autopsy have not been numerous. Of eight of Brøchner-Mortensen's patients who came to autopsy, four showed slight to moderate cirrhotic changes; three had used alcohol excessively and a diagnosis of Banti's disease was made on the fourth.<sup>43</sup> Two more recent cases studied at autopsy have shown no hepatic findings of note.<sup>46, 47</sup> A patient with gout and chronic anemia reported by Lambie and Davies<sup>48</sup> was found only to have evidence of mild chronic passive congestion. One patient, known to have consumed large quantities of beer as well as one pint of whiskey daily, showed typical alcoholic cirrhosis.<sup>49</sup> In summary, seven of the cases reviewed in this paragraph were free of etiological factors which might have been expected to lead to hepatic impairment. In only one of these seven (Brøchner-Mortensen's patient with Banti syndrome) was a significant degree of hepatic involvement noted.

Injection of liver extract has been followed by acute gouty arthritis.<sup>43, 55 through 61</sup> Although some investigators considered this evidence of hepatic involvement in gout,<sup>55</sup> there is reason to believe that the responsible mechanism is more closely related to the effect of liver extract upon hematopoiesis.<sup>61</sup> Similarly, the occurrence of acute hepatomegaly as a prodrome of an attack of acute gouty arthritis<sup>62, 63</sup> is neither sufficiently common nor is its pathogenesis sufficiently well-understood to be taken as evidence of hepato-cellular involvement.

Both from our data and from a review of the literature, it appears that, except in the presence of a complicating disease process, the liver is ordinarily functionally and anatomically normal in gout. Since this is the case, diffuse liver disease cannot be either the cause of gout, or a frequent visceral complication of gout.

#### SERUM PROTEINS IN GOUT

Our data showed no consistent abnormalities in total protein values, although occasional values somewhat above the upper limit of normal were observed. Abnormalities in the components distinguished by fractionation was likewise unusual in uncomplicated cases. When patients with hepatic or renal impairment were considered, they were found to have a significant decrease in the true A/G ratio. The decrease was due chiefly to a decrease in the albumin fraction, and small increases in the various globulin fractions.

These data appear consistent with those reported by previous investigators. The 36 patients studied by Talbott<sup>64</sup> had an average serum total protein concentration of 7.13 gm. per cent. Four patients studied by Scull, Bach and Pemberton<sup>65</sup> had an average total protein of 7.27 gm. per cent, while three reported by Aldred-Brown and Munro<sup>66</sup> had an average serum protein of 6.69 gm. per cent. The A/G ratios (Howe method) in the latter two series average 1.80 and 1.69 respectively. We have not determined plasma fibrinogen, but both Aldred-Brown and Munro<sup>66</sup> and Mester<sup>67</sup> reported elevations in plasma fibrinogen which were correlated with acceleration of the sedimentation rate.

Apart from the elevated plasma fibrinogen concentrations, no quantitative abnormalities in serum proteins have been demonstrated to occur in uncomplicated gout. Hepatic or renal impairment produces expected changes in protein patterns. A few patients, particularly in the active phases of articular involvement, give evidence of qualitative alterations in protein components by the finding of abnormal globulin reactions. Nevertheless, the changes are slight, and neither qualitative nor quantitative alterations in serum protein components appear to be usual in uncomplicated gout.

#### SERUM CHOLESTEROL CHANGES DURING GOUTY ARTHRITIS

Although serum cholesterol partition gives no evidence of liver damage in gout and the older belief that hypercholesterolemia is frequent in gout appears to have been incorrect, the pronounced decrease in serum cholesterol levels during acute gouty arthritis is of considerable interest.

The increased output of adrenocortical sex and metabolic steroids which occurs when the adrenal is stimulated by pituitary adrenocorticotrophin is associated with a simultaneous depletion of adrenal cholesterol esters.<sup>97</sup> Since the conversion of isotopically labelled cholesterol to a labelled hormonal steroid, progesterone, has already been demonstrated in vivo, it appears probable that the adrenal cholesterol esters are the immediate substrate for the formation of the hormonally active steroids of the adrenal. After the adrenal cholesterol esters are depleted by severe stress or following the administration of pituitary adrenocorticotrophin, the serum cholesterol level falls<sup>98</sup> and the level rises following administration of desoxycorticosterone or adrenal cortical extract.<sup>99</sup> These observations suggest that the serum cholesterol may be the ultimate substrate for adrenal steroid formation and, in addition, that the serum cholesterol level responds acutely to changes in the rate of active steroid formation by the adrenal cortex.

The fall in serum cholesterol during acute gouty arthritis is thus consistent with a hypothesis of increased adrenal cortical steroid output during the acute gouty attack. Recent additional observations<sup>100</sup> suggest that the serum cholesterol of gout patients tends to be highest just before the onset of acute gouty arthritis. High levels may persist for some time after the onset. This need not mean that increased adrenocortical activity does not precipitate

the attack since the experimental observations indicate that, in severe stress, serum cholesterol does not fall for some time. Apparently the store of cholesterol esters in the adrenal must be depleted before serum cholesterol is utilized.<sup>101</sup>

The finding of a prodromal peak in serum cholesterol values, which suggests a decreased production of adrenocortical steroids according to the above schema, is consistent with other biochemical findings indicating decreased adrenocortical activity to precede the acute gouty attack. The urate clearance, the absolute output of urinary urate, and the ratio of urine urate to urine creatinine, are all increased under conditions of increased adrenocortical function.<sup>102, 103</sup> All are decreased in the prodromal period before acute gouty arthritis.<sup>104, 105, 106</sup> Talbott, Jacobson and Oberg<sup>107</sup> also demonstrated the occurrence of diuresis with sodium and chloride excretion in excess of water during the prodromal period, with a negative sodium and chloride balance suggestive of adrenocortical insufficiency.

The hypothesis that temporary functional adrenocortical hypofunction precedes, and sets the stage for, the acute gouty attack has received additional support from recent studies with pituitary adrenocorticotrophin. Robinson, Conn, Block and Louis<sup>108</sup> have reported that when pituitary adrenocorticotrophic hormone was administered to a gouty subject, an attack of gout occurred some days after cessation of hormone administration. The time of the attack corresponded to the beginning of recovery from a functional adrenocortical depression which regularly occurs after adrenocorticotrophin administration is halted. Gout attacks occurring after cessation of adrenocorticotrophin administration have also been noted by Leiter and his co-workers.<sup>109</sup> These observations on induced attacks, like the changes in serum cholesterol, urate metabolism, and electrolyte turnover, suggest that a prodromal depression in adrenocortical steroid output sets the stage for the gout attack and that the onset of the attack is associated with a reactive increase in some adrenocortical function. It is possible that, by reflecting these changes, alterations in serum cholesterol may aid in predicting periods of increased susceptibility to gout attacks.

### SOME COMPARATIVE FEATURES OF GOUT AND RHEUMATOID ARTHRITIS

Only in occasional cases<sup>68, 69, 70</sup> is it difficult to differentiate gout from rheumatoid arthritis. Nevertheless, because of the important articular disturbances with which both these systemic diseases are associated, it is important to study the resemblances and differences in their clinical pathology. A number of prominent features are tabulated in table 5.

Abnormalities in circulating proteins are prominent in the clinical pathology of rheumatoid arthritis and are reflected in decreased A/G ratios,<sup>65, 66</sup> in altered electrophoretic patterns,<sup>71 through 75</sup> in abnormal globulin tests,<sup>75, 78 through 81</sup> in elevated sedimentation rates,<sup>66, 75, 81, 82</sup> in altered non-specific precipitation and agglutination reactions<sup>81, 85, 86, 87, 111</sup> and occasion-

TABLE V

## Some Clinical Pathological Features of Gout and Rheumatoid Arthritis

(Where no reference number is given in the table, the findings are those discussed in the text or based upon unpublished data from our group of gout patients. The term "complicated" used with reference to certain of the findings in gout, refers to data obtained in the group of patients with gout and known complicating disease.)

	Gout	Rheumatoid Arthritis
1. Plasma urate	Elevated in 90% of cases	Normal in 90% of cases
2. Serum total protein	Average 105% of normal controls	Average 98% of normal controls <sup>65,66</sup>
3. A/G ratio (Howe)	Average 106% of normal controls	Average 76% of normal controls <sup>65,66</sup>
4. Electrophoretic or chemical fractionation	Normal in uncomplicated cases. With hepatic damage, increases in beta- and gamma-globulin. With renal damage, increases in alpha- and gamma-globulin	Early active cases have elevated alpha-globulin. Late active cases and Still- Feltz syndromes have elevated alpha- and gamma-globulin <sup>71</sup> through <sup>76</sup>
5. Plasma fibrinogen	In chronic gouty arthritis, average is 158% of normal controls	In chronic active cases, average is 135% of normal controls <sup>65,67</sup>
6. Plasma volume	No data available	Reported increased, "hydreic syndrome" <sup>77,78</sup>
7. Plasma viscosity	No data available	Increased, roughly parallel to clinical judgment of activity <sup>79</sup>
8. Sedimentation rate	Normal in interval gout. Increased in acute gouty arthritis after first 24 hours and in chronic gouty arthritis	Increased, except in "burned-out" and inactive cases <sup>82,86,83,84</sup>
9. Thymol turbidity	15% abnormal in interval gout, 28% in active gouty arthritis, 90% in complicated cases	Abnormal in 36% of proved cases <sup>80</sup>
10. Thymol flocculation	Normal in 98% of observations	No data available
11. Cephalin flocculation	Normal in interval gout, 33% abnormal in active gouty arthritis, 42% in complicated cases	Abnormal in 75% of proved cases <sup>81</sup>
12. Colloidal gold flocculation	Normal in interval gout, 25% abnormal in active gouty arthritis	Abnormal in 78% of proved cases <sup>80,110</sup>
13. Plasma formol-gel reaction	Negative when sedimentation rate is normal. Abnormal when sedimentation rate is elevated <sup>83</sup>	Abnormal in 25% of mild cases, 44% of moderate cases, 94% of severe cases
14. Serum formol-gel reaction	May be normal although sedimentation rate is accelerated <sup>82</sup>	Usually abnormal when sedimentation rate is elevated <sup>82</sup>
15. Weltmann reaction	Shortened, when sedimentation rate is elevated <sup>82,83</sup>	Abnormal in 25% of mild cases, 44% of moderate cases, 71% of severe cases <sup>82,83</sup>
16. Other findings related to abnormal serum proteins	None reported	Abnormal nonspecific serological reactions, cryoglobulinemia, acrocyanosis, amyloidosis <sup>86</sup> to <sup>92</sup>
17. Liver function tests unrelated to serum proteins	Normal in interval gout and in active gouty arthritis	Abnormalities demonstrable in up to 72% of patients, depending on tests used <sup>94,95</sup>

ally in more bizarre types of reactions associated with abnormal globulins such as cryoglobulinemia, acrocyanosis and amyloidosis.<sup>88, 89, 90, 91</sup> Gibson and Pitt<sup>81</sup> suggest that an increased concentration of non-rouleaux forming globulins of low molecular weight (alpha-globulins?) might account for the increased plasma volume reported in certain cases of rheumatoid arthritis.<sup>76, 77</sup>

Gibson and his coworkers<sup>82, 83</sup> have presented interesting data on the formol-gel reaction which aid in understanding the different alterations in circulating protein in gout and rheumatoid arthritis. In both diseases, when the sedimentation rate is elevated, the *plasma* formol-gel reaction is generally abnormal. In rheumatoid arthritis, when the sedimentation rate is elevated, the *serum* formol-gel reaction is also generally abnormal, but in gout it is usually normal. These findings, which agree with the data of Miles and Salt,<sup>53</sup> suggest that increased plasma fibrinogen may be the sole determinant of the increased sedimentation rate of active gouty arthritis,<sup>66, 67</sup> while the accelerated sedimentation rate in rheumatoid arthritis is accompanied by more complex changes in serum globulin structure.

There is, finally, considerably more evidence of hepatocellular involvement in rheumatoid arthritis than in gout<sup>94, 95</sup> which may aid in explaining the well-known intolerance of rheumatoid arthritis patients to cinchophen.<sup>96</sup>

Both the evidence for a diversified series of changes in circulating proteins and the direct evidence for hepato-cellular impairment in rheumatoid arthritis suggest that involvement of the liver and of the reticulo-endothelial system are both more frequent and more severe in rheumatoid arthritis than in gout.

### CONCLUSIONS

Sensitive liver function tests indicate that gout is not uniformly associated with functional hepatic impairment. Diffuse liver disease can therefore neither be the cause of gout nor a uniform consequence of gout. Abnormal liver function tests are rare in uncomplicated interval gout. Most of the abnormalities are found to occur in patients with known complicating disease and, in these patients, the degree of functional hepatic impairment is commensurate with the nature and severity of the associated disease.

Patients with active gouty arthritis (acute, subacute, or chronic) occasionally show abnormal findings. These are relatively infrequent and almost entirely limited to those function tests dependent on alterations in serum globulins. Since serum globulins are produced by the entire reticulo-endothelial system, these findings may not alone be taken to prove hepatocellular involvement. The abnormalities noted in patients with known complicating disease are not limited to the globulin tests. This suggests that the altered results in active gouty arthritis are in fact due to reticulo-endothelial irritation, and not to hepato-cellular involvement.

Values for serum total protein and for the individual serum protein fractions are normal in uncomplicated gout. The occurrence of severe renal or hepatic impairment produces changes in the protein pattern which are in the expected direction.

Serum cholesterol values and partition are usually normal in gout. The older reports of hypercholesterolemia in this disease appear to have been based upon incomplete knowledge of the wide normal range of serum cholesterol levels. Serum cholesterol levels are significantly lower in acute gouty arthritis than in interval gout and preliminary data suggest that a peak value occurs before the onset of acute gouty arthritis. When considered with other known biochemical changes during the gout cycle, the cholesterol changes are compatible with an endocrine hypothesis of decreased prodromal adrenocortical steroid formation and increased formation of some type of steroid during the attack.

Evidence now available suggests that diffuse hepatic involvement and alterations in circulating protein are not fundamental to the pathogenesis of gout.

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# TRANSIENT "0" DIASTOLIC BLOOD PRESSURE (INDIRECT) IN THE UPPER EXTREMITIES \*

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RECENTLY Wilburne<sup>1</sup> described a benign cardiovascular syndrome, the most prominent features of which were transient "0" brachial diastolic pressure, normal or elevated popliteal pressure, tachycardia and nervous tension occurring usually in young adults. He felt that the syndrome was psychosomatic in nature and that although the true brachial diastolic pressure probably was not "0", in all likelihood it was subnormal. The reduced diastolic pressure in the brachial arteries appeared to be due to peripheral vascular dilatation. The presence in the lower extremities of normal or increased pressure was considered to represent a compensatory phenomenon directed towards the maintenance of cerebral flow.

My observations suggest that this syndrome is not infrequently encountered. Following are brief summaries of five cases.

## CASE REPORTS (See Table 1)

*Case 1.* An emotionally unstable 19 year old white soldier was referred to the Cardiac Clinic because of brachial diastolic pressure of "0". Physical examination, electrocardiographic and fluoroscopic studies revealed no evidence of cardiovascular disease. Initial brachial readings were 140/0 mm. Hg and associated popliteal prone pressure was 190/90 mm. Hg; heart rate was 116. Continuous observation disclosed a return of the brachial diastolic pressure to 60 mm. Hg at the end of three to four minutes. The systolic pressure exhibited an 8 mm. drop to 132 mm. Hg. The popliteal prone pressure was 180/82 mm. Hg and the heart rate 100. Fifteen minutes later the brachial reading was 130/74 mm. Hg; the popliteal prone pressure was 175/80 mm. Hg and the heart rate was 96. Observation over a period of two hours disclosed a distinct tendency to frequent fluctuation in the brachial diastolic readings between normal and "0".

*Case 2.* A 19 year old white soldier complained of "nervousness," dizziness, easy fatigability and occasional vomiting spells. At times he awakened at night gasping for breath and felt his heart beating very rapidly. Physical examination, electrocardiogram and roentgenogram failed to reveal any cardiac abnormalities. Initial blood pressure readings were 160/0 mm. Hg to 170/50 mm. Hg (these changes occurred within a 10 second interval during the time of initial auscultation). Fifteen to 30 minutes later the brachial pressure averaged 134/62 mm. Hg. The lower extremity reading was 154/110 mm. Hg.

*Case 3.* A 19 year old white soldier stated that for years he had been "nervous," his heart beat rapidly and he became "dizzy" on exertion or excitement. He had also noted intermittent pain in the left chest bearing no relation to effort. He had been told that he had some elevation of his blood pressure since an attack of "flu" four years previous. On examination his breathing showed irregularities as to rate and depth. Complete studies disclosed no abnormal cardiac findings. The electrocardiogram revealed a sinus tachycardia.

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TABLE I

	Patient	Age (Years)	Time	Brachial Blood Pressure (mm. Hg)	Popliteal Pressure (mm. Hg)	Pulse Rate
1	J. B.	19	Initial	$\frac{140}{0}$	$\frac{190}{90}$	116
			3-4 min. later	$\frac{132}{60}$	$\frac{180}{82}$	100
			15 minutes later	$\frac{130}{74}$	$\frac{175}{80}$	96
2	F. A.	19	Initial	$\frac{160}{0}$		
			10 seconds later	$\frac{170}{50}$		
			15-30 min. later	$\frac{134}{62}$	$\frac{154}{110}$	
3	H. Z.	19		left $\frac{176}{0}$	$\frac{194}{140}$	114-130
			1 minute later	right $\frac{174}{40}$	$\frac{180}{140}$	
4	— S.	27		$\frac{140-180}{0}$	$\frac{220}{80-120}$	110
5	S. B.	24	Initial	$\frac{184}{0}$	$\frac{200}{90-105}$	96
			15 minutes later	$\frac{152}{72}$	$\frac{210}{110}$	92

Blood pressure in his left arm was 176/0 mm. Hg, in the right arm 174/40 mm. Hg, in the left leg 194/140 mm. Hg, and in the right leg 184/140 mm. Hg. The ventricular rate varied between 114 and 130. The differences in the right arm and left arm readings may have represented a tendency to recovery, since the right arm determination was made approximately one minute after that obtained in the left arm.

*Case 4.* A 27 year old white soldier stated he had always had a "nervous disposition." He tired and became excited easily and on prolonged standing he became weak, dizzy and occasionally fainted. On induction he was told of a transient elevation of his blood pressure.

Complete cardiac studies including electrocardiogram, roentgenograms and fluoroscopy were entirely negative for organic disease.

Blood pressures in both arms showed a systolic variation between 140 and 180 mm. Hg while the diastolic pressure was "0". Popliteal pressure was 220/80 to 120 mm. Hg. The pulse rate was 110.

*Case 5.* A 24 year old soldier, with no complaints, on routine examination by his unit dispensary medical officer was found to have a low diastolic blood pressure. Because of this he was referred to the cardiac clinic for consultation. On examination at the cardiac clinic the blood pressure in the upper extremities was 184/0 mm. Hg and in the lower limbs 200/90 to 105 mm. Hg. His heart rate was 96. Fifteen minutes later the brachial pressure had changed to 152/72 mm. Hg, popliteal pressure to 210/110 mm. Hg and pulse rate to 92.

History, physical examination, electrocardiogram, fluoroscopy and roentgenography revealed no evidence of heart disease.

### DISCUSSION

These observations are in close accord with those reported by Wilburne.<sup>1</sup> All five patients were young adults. Four presented evidence of autonomic nervous system imbalance. All revealed transitory "0" brachial diastolic pressure with normal or elevated popliteal pressure and tachycardia. A "pistol shot" sound was noted in each case. In Wilburne's series the "pistol shot" sound occurred in 15 of the 38 cases. The search for a diastolic murmur was conducted in various positions and phases of respiration. None could be demonstrated. Blood pressure determinations were performed with a standard sphygmomanometer, care being taken to avoid pressure upon the vessel with the stethoscope, since false low diastolic readings may occasionally be obtained under such circumstances.

As regards the mechanisms involved in the production of this syndrome, it is well established that fear<sup>2</sup> or psychic disturbance may produce unusual cardiovascular manifestations,<sup>3, 4</sup> probably mediated via the autonomic nervous system. Apparently the cases reported here represent centrally initiated vasomotor effects in which the upper extremities exhibit vasodilatation and the lower extremities compensatory vasoconstriction, the latter in order to maintain cerebral flow (Wilburne). Evidence for such compensatory phenomena appears to exist.<sup>5, 6</sup> Failure of this compensatory mechanism may eventuate in syncope.

It is important that this non-pathologic syndrome be distinguished from aortic regurgitation. The transient character of the indirect "0" diastolic reading obtained in the arms, together with the absence of a diastolic murmur, cardiac enlargement and of low diastolic pressure in the lower extremities easily points to the correct diagnosis. The history is frequently of additional aid. If suggestive of rheumatic fever or syphilis it may support a diagnosis of aortic insufficiency; conversely, a history of emotional instability would favor the non-pathologic syndrome. Electrocardiographic, roentgenologic and serologic studies may be of further aid in the differential diagnosis.

### SUMMARY

1. Five males, aged 19 to 27 years, exhibiting the syndrome of "0" brachial diastolic pressure, normal or elevated popliteal pressure and tachycardia, are presented.

2. Four of the five showed definite psychoneurotic traits with various manifestations of autonomic nervous system imbalance.

3. None presented evidence of any organic cardiac disease despite extensive studies, including fluoroscopy, roentgenography and electrocardiography.

4. It is important that this benign syndrome be distinguished from aortic insufficiency. The absence of a diastolic murmur, cardiac enlargement, and of low diastolic pressure in the lower extremities, together with the transient character of the indirect "O" diastolic reading in the arms, will easily preclude an erroneous clinical diagnosis of aortic insufficiency. The history is often of assistance. At times electrocardiograms, roentgenograms and serologic studies may provide additional information.

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# INTERMITTENT DOSAGE SCHEDULES OF STREPTOMYCIN WITH RESULTANT PROLONGED SENSITIVITY OF *M. TUBERCULOSIS*\*

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CURRENT streptomycin treatment regimens for pulmonary tuberculosis have been dictated largely by streptomycin toxicity and by development of bacterial resistance to this antibiotic. Since the initial utilization of streptomycin as an adjunct to the treatment of tuberculosis,<sup>9, 8</sup> the general trends to minimize or eliminate these obstacles have been toward reductions in daily dosage, frequency of administration, and duration of treatment. These trends have effected a reduction of toxicity; however, the latter trend has been utilized to avoid rather than to solve the paramount obstacle of prolonged effective treatment, namely the development of bacterial resistance. This, in our opinion, has resulted in some sacrifice of the full therapeutic potentialities of streptomycin. The following review of treatment trends provides some rationale for the intermittent dosage schedules employed in this study, which, according to our observations, currently represent the most successful approach to this problem.

## TREATMENT TRENDS

Since the initial investigations, daily dosage schemes of streptomycin in the treatment of pulmonary tuberculosis have been governed largely by protocols issued by joint committees representing numerous groups of investigators. In May, 1946, September, 1946, December, 1946, and November, 1947, these committees recommended a daily dosage of 1.8, 1.5 to 3.0, 2.0, and 1.0 to 2.0 grams respectively.<sup>16, 17</sup> Muschenheim and his group,<sup>13</sup> in December, 1947, reported several cases of pulmonary tuberculosis treated on the one gram dosage previously recommended as therapeutically satisfactory by the Mayo Group.<sup>8</sup> At Fitzsimons General Hospital the one gram plan was investigated between August and November, 1947, and then adopted routinely, because it reduced toxicity and resulted in clinical improvement comparable to that of the previous two gram schedule. Exten-

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sive studies are being made of a one-half gram daily dosage, but the results are not completely established.\*

A review of the streptomycin dosage plans, from the initial one to three grams per diem<sup>8</sup> to the currently accepted one gram per diem, reveals the trend toward a decreased daily dosage. Since similar clinical results have been observed in all plans, the wide range of daily dosages effective in humans has further substantiated Feldman's<sup>5</sup> observation, based on experiments with guinea pigs, that this antibiotic has a broad therapeutic index, the full limitations of which are not well established.<sup>4,2</sup>

The second recent trend in the treatment of tuberculosis with streptomycin has been a decrease in the frequency of its daily administration. The protocols issued in May and December, 1946, recommended injections every four hours.<sup>17</sup> In July, 1946, Feldman<sup>5</sup> concluded, from experiments on tuberculous guinea pigs, that frequent injections of streptomycin were not essential for full therapeutic results. In May, 1947, Feldman, Hinshaw and Karlson<sup>6</sup> reported administering streptomycin in two daily doses. The protocol published in November, 1947, recommended injections every four to six hours, admitting that, "It is not known how frequently intramuscular injections need be made. . . ."<sup>17</sup> At Fitzsimons General Hospital we have administered streptomycin twice daily since October, 1947, with no apparent loss of effect. In December, 1947, the Cornell group<sup>13</sup> reported administering streptomycin in a single daily injection. Although the action of infrequently administered streptomycin on *M. tuberculosis* is not understood, this trend indicates that constantly maintained blood levels are not essential.

The third trend, a decrease in the duration of treatment, is being stressed currently. The original clinical work included a treatment period of two to six months,<sup>8</sup> while the protocols of May, 1946, and December, 1946, recommended 120 days. In the report of November, 1947, however, the Council on Pharmacy and Chemistry<sup>17</sup> recognized the problem of bacterial resistance in relation to duration of treatment by stating that strains of resistant tubercle bacilli probably appear in at least two-thirds of patients after less than 120 days of streptomycin administration; they concluded, "It is not known . . . how long treatment should be continued." In December, 1947, the Cornell group<sup>13</sup> reduced the treatment period from 120 to 42 days, realizing that some therapeutic benefit probably was sacrificed, to prevent the development of resistance.

## RESISTANCE

Sensitivity of *M. tuberculosis* to streptomycin in vitro was proved first by Schatz and Waksman.<sup>14</sup> Because Buggs<sup>1</sup> reported the development of increased resistance of bacteria other than tubercle bacilli to streptomycin, Youmans<sup>20</sup> studied the problem in relationship to *M. tuberculosis* and concluded that streptomycin resistance developed in vivo and in vitro. These

\* This study is now in progress at Fitzsimons General Hospital.

observations were later confirmed at Fitzsimons General Hospital by studying the bacteriology of several hundred tuberculous patients treated with streptomycin. By examining cultures from these patients, it was ascertained that tubercle bacilli, originally inhibited by minute amounts of streptomycin, at a later date were capable of growth in vitro in large concentrations of the antibiotic. In these cases the organisms were classed as streptomycin resistant. The actual defining borderline between a therapeutic state of "resistance" and "sensitivity" was first proposed by Steenken<sup>15</sup> based on results of guinea pig experiments. He found that strains of tubercle bacilli that could grow in 10 or more micrograms of streptomycin per milliliter of test medium were therapeutically resistant in guinea pigs. Using this criterion, the following facts became evident: (1) Resistant organisms were found in approximately 75 per cent of streptomycin treated patients on the one and two gram schedules. (2) These resistant organisms appeared in most cases after 35 to 50 days of therapy. (3) The characteristic of resistance was apparently permanent.\*

A number of investigators<sup>10, 19</sup> demonstrated that resistant organisms isolated from patients treated with streptomycin and injected into laboratory animals were not influenced by further administration of the drug. Furthermore, the Cornell group<sup>11, 13</sup> have suggested that a definite correlation exists between sensitivity and response of tubercle bacilli to streptomycin therapy in humans. In a study of seven patients they noted definite evidence of the infections' regression during the first weeks of treatment, when the organisms were highly sensitive to the drug in vitro; however, "at a variable interval after the first detection of drug resistant bacilli, the tuberculous infections again became actively progressive. In every instance the newly progressive infections were completely uninfluenced by the further administration of streptomycin. . . ." The grave potentialities of streptomycin resistance in tuberculosis might be inferred from the work of several investigators who suggested an actual enhancement of the pathogenicity of resistant strains of gonococcus, meningococcus, and *B. abortus* subjected to continued streptomycin therapy.<sup>12, 7</sup>

Two of the three trends previously described, namely, reduced dosage and decreased frequency of injections, seem pharmacologically sound, because the problem of toxicity has been minimized; however, the third trend, a shortened period of treatment, has not satisfactorily approached the problem of resistance because it may conceivably result in some sacrifice of streptomycin's therapeutic value. Since a prolonged period of administration of streptomycin is theoretically necessary for maximum benefits,<sup>5</sup> a treatment regimen which would further reduce the problem of toxicity, prolong bacterial sensitivity and consequently extend the effective treatment period, in our opinion merits investigation.

\* Myron W. Fisher, 1st Lt., M.S.C., unpublished data.

## ANIMAL EXPERIMENTS

A plan attempting to accomplish these objectives in humans has evolved chronologically from animal experiments. The inference that the effect of streptomycin is persistent and not dependent upon high blood levels insured by frequent injections, was first made by Feldman.<sup>5</sup> He observed that the effectiveness of streptomycin in tuberculous guinea pigs was not appreciably diminished either by infrequent daily injections or by inoculations four times daily on alternate weeks.

In a series of preliminary experiments Corper and Cohn<sup>3</sup> further substantiated these results. In their first study a group of guinea pigs, treated with streptomycin for 82 to 91 days and then infected with strains of human tubercle bacilli, lived an average of 29 days, whereas a control group lived an average of 22 days. Neither group received streptomycin following the induced infections. This experiment indicated that streptomycin in tuberculous guinea pigs does not act as a "simple therapeutic retardant," but, rather, seems to exert a "threshold of remote sustained action." With this result in mind, these investigators performed a study of intermittent dosages in guinea pigs. When 25,000 streptomycin units were given to one group of guinea pigs in four daily divided doses, to a second group in one daily injection, to a third in one injection every fifth day, and to a fourth group in one injection every tenth day, the average duration of life following infection with strains of human tubercle bacilli amounted to 125, 100, 100, and 70 days respectively as compared to 20 days for the controls.

With a favorable therapeutic response to intermittent streptomycin administration apparent in guinea pigs, the following experiment was set up at Fitzsimons General Hospital in an attempt to substantiate these findings in humans.

## REPORT OF 16 CASES

This report represents observations on 16 patients with pulmonary tuberculosis receiving intramuscular streptomycin therapy by intermittent dosage schedules at Fitzsimons General Hospital during the five month period from August 15, 1947 to January 20, 1948. All patients were observed for a period of at least one month prior to the initiation of streptomycin. Because sensitivity studies were a necessity in this experiment, 50 per cent of the patients were selected from the far advanced cavitory group to provide positive cultures throughout and after therapy. All patients were positive bacteriologically by direct smear or culture before streptomycin was given.

Strict bed rest was required before, during, and after treatment. Streptomycin was given intramuscularly, two grams in five divided doses, every third day in eight cases, every fourth day in one case, and every fifth day in seven cases.

No patient received collapse therapy before or during antibiotic therapy except one (B.), in whom pneumothorax was initiated after 90 days of strep-

tomycin administration. Following treatment, collapse measures were used when indicated. In addition, multivitamins, cod liver oil cocktails, and 300 mg. ascorbic acid were prescribed daily.

These patients were studied clinically by three of the authors, and the sensitivity studies were carried out by a fourth.\* Special clinical emphasis was placed on weekly evaluations of streptomycin toxic reactions, cough, sputum quantity and quality, and weight. Temperature and pulse were recorded five times daily. Caloric and vestibular function tests were performed on all patients, except two, after treatment.

Roentgen-ray studies were made throughout the period of observation as follows: (1) stereoscopic views before treatment, on initiation and completion of therapy, and monthly throughout hospitalization, and (2) special films when indicated. In this experiment material for tubercle bacilli cultures was submitted weekly during hospitalization, and sensitivity studies were done, using Herrold's medium, on all positive cultures. Wintrobe sedimentation rates, complete blood counts, and urinalyses were done bi-monthly.

These cases were evaluated at monthly intervals with a concluding analysis in the post treatment period. (See accompanying table.)

### SUMMARY OF RESULTS

- I. Clinical response
  - A. Excellent results were obtained in seven cases ✓
  - B. Moderate results were obtained in six cases
  - C. Minimal results were obtained in three cases
- II. Roentgenological response
  - A. Excellent results were obtained in eight cases ✓
  - B. Moderate results were obtained in four cases
  - C. Minimal results were obtained in four cases
- III. Bacteriological status
  - A. Conversion occurred during treatment in eight cases
  - B. Tubercle bacilli became streptomycin resistant in one case
  - C. Tubercle bacilli remained streptomycin sensitive in seven cases
- IV. Toxicity.
  - A. No cases in this series showed subjective signs of streptomycin toxicity

### DISCUSSION

Theoretically, an ideal chemotherapeutic agent for the treatment of tuberculosis would be one which, by continuous suppressive and retardant action on *M. tuberculosis*, would eventually allow the body to gain ascendancy and heal the infection. Streptomycin is an antituberculous agent of considerable potency; however, the prolongation of its suppressive action is

\* M. W. F.

Analysis of 16 Patients Treated by Intermittent Streptomycin Dosage Regimens

Treatment Schedule	Diagnosis	Patient and Race	(1) Clinical Onset in Mos.	Clinical and Pre- sumed Pathological Character of Lesion	Complications	Total Days Treatment	Total Grams SM	Clinical Response (2)										X-Ray Response (3)		In- dications for SM (4)	Collapse		Final Analysis 1-4 Months After Streptomycin (6)					
								Temperature		Cough		Sputum Volume in c.c.		Weight		Gen. Cond.		Sed. Rate			Stability	Cavity Diam. in cm.	Made Feas- ible	(5) Ef- fected	Clinical Response	X-ray Response	Bacterio- logical Status	
								Be	Af	Be	Af	Be	Af	Be	Af	Be	Af	Be	Af									
Mod. adv.	Mod. adv.	A (w)	2	Patchy pneumonic	Emphy- sema	66	44	C	A	Mod.	No	No	0	60	0	121	147	G	F	G	48W	7W	Reg.			Ex.	Mod.	Conv.
		B (w)	10	Patchy pneumonic with thin walled cavity		90	60	B	A	Min.	No	No	5	0	170	167	G	G	G	8W	3W	Reg.	1+	0		Min.	Mod.	Conv.
		C (c)	3	Patchy pneumonic with thin walled cavity		120	80	B	A	Min.	Min.	Min.	5	2	153	172	G	G	G	36W	3W	Reg.	4+	0		Mod.	Ex.	Pos. (S)
2 gm. q 3 days	2 gm. q 3 days	D (w)	2	Chr. type—fibrocav- ernous with sec. chgs.		69	46	A	A	Sev.	Min.	Min.	120	30	171	188	G	G	G	52W	17W	Reg.	4+	4+		Ex.	Min.	Pos. (S)
		E (c)	3	Patchy pneumonic with thin walled cavity		120	80	B	A	Mod.	Min.	Min.	60	5	143	180	F	G	G	20C	10W	Reg.	4+	3+		Ex.	Mod.	Pos. (S)
		F (w)	3	Patchy pneumonic with annular cavity		120	80	A	A	Min.	No	No	15	0	165	186	G	G	G	23C	4W	Reg.	2+	0		Mod.	Mod.	Conv.
Far adv.	Far adv.	G (c)	2	Confluent pneumonic with cavitation		120	80	D	A	Sev.	Mod.	Mod.	120	120	112	120	F	G	G	44W	17W	Reg.	3+	1+		Mod.	Ex.	Pos. (S)
		H (w)	6	Chr. type—fibrocav- ernous with sec. chgs.		120	80	A	A	Mod.	Min.	Min.	45	15	130	138	F	G	G	48W	2W	Reg.	4+	4+		Mod.	Min.	Pos. (S)

2 gm.  
q  
3 days

# Analysis of 16 Patients Treated by Intermittent Streptomycin Dosage Regimens—Continued

Treatment Schedule	Diagnosis	Patient and Race	(1) Clinical Onset in Mos.	Clinical and Pathological Character of Lesion	Complications	Total Days Treatment	Total Grams SM	Clinical Response (2)										X-Ray Response (3)			Indications for SM (4)	Collapse		Final Analysis 1-4 Months After Streptomycin (6)					
								Temperature		Cough		Sputum Volume in c.c.		Weight		Geo. Cond.		Sed. Rate		Stability		Cavity Diam. in cm.		Made Feasible	(5) Effected	Clinical Response	X-ray Response	Bacteriological Status	
								Be	Af	Bo	Af	Be	Af	Be	Af	Bo	Af	Be	Af	Bo		Af	Be						Af
2 gm. q 4 days	Mod. adv.	I (w)	3	Patchy pneumonic	Hemorrhage	120	60	A	A	Min.	No	Af	Be	Af	G	27W	4W	Reg.	Reg.	Reg.			Mod.	Ex.	Conv.				
		J (w)	2	Patchy pneumonic	Hemorrhage	65	26	A	A	No	No				G	13W	3W	Reg.	Reg.			Mio.	Ex.	Pos. (S)					
		K (c)	1	Patchy pneumonic with annular cavity	Pleurisy	120	48	C	A	Mod.	Min.	15	3	100	111	F	15W	4W	Sta.	Reg.	2+	2+	Yes	Pending	Ex.	Mod.	Pos. (R)		
2 gm. q 5 days	Mod. adv.	L (e)	2	Chronic productive		120	48	A	A	Mod.	Min.	60	0	132	132	G	24W	4W	Sta.	Reg.			Min.	Min.	Conv.				
		M (w)	7	Patchy pneumonic with thin walled cavity		120	48	B	A	Mod.	Min.	60	5	163	183	G	21W	6W	Sta.	Reg.	2+	0	Yes	Pt. Pending	Ex.	Conv.			
		N (w)	18	Fibrocavernous with recent exud. spread	Hemorrhage	90	30	A	A	Sev.	Min.	120	5	134	150	F	42W	5W	Proz.	Reg.	2+	0	Yes	Pt. AMA	Ex.	Conv.			
Far adv.	Far adv.	O (c)	1	Confluent pneumonic		120	48	D	A	Sev.	No	240	0	113	132	P	59W	7W	Prog.	Reg.			Yes	Ppn.	Ex.	Ex.	Pos. (S)		
		P (w)	36	Fibrocavernous with secondary changes		120	48	A	A	Mod.	Min.	60	5	156	160	G	6W	4W	Sta.	Reg.	4+	4+	Yes	Pt.	Mod.	Min.	Conv.		

- (1) Clinical onset in months: The interpretation is as follows: Duration of disease prior to streptomycin therapy.
- (2) Clinical response: The interpretation is as follows: Be—Before streptomycin therapy. Af—After streptomycin therapy. Temperature—According to NTA classification. General Condition: P—Poor. F—Fair. G—Good.
- (3) X-Ray response: The interpretation is as follows: Be and Af: As above. Sta.—Stationary. Reg.—Regressive. Prog.—Progressive.
- (4) Indications for streptomycin: The interpretation is as follows: Prep.—Preparatory for surgery. Defin.—Definitive with bedrest. Panic—Prognosis extremely poor.
- (5) Collapse effected: The interpretation is as follows: Ppn—Pneumoperitoneum. Pt—Pneumothorax. Thora—Thoracoplasty. AMA—Patient left against medical advice.
- (6) Final analysis: Interpretation of bacteriological status as follows: Conv.—Sputum converted from positive to negative. Pos.—Sputum positive. (S)—Sensitive to streptomycin in vitro. (R)—Resistant to streptomycin in vitro.

limited by the development of bacterial resistance. It is logical, therefore, to assume that were the resistance problem eliminated, thereby permitting effective administration of streptomycin for an indefinitely long period, its continued suppressive action would ultimately permit ascendancy of natural healing factors. According to our observations, except in one instance the intermittent dosage schedules have prolonged bacterial sensitivity and have thus lengthened the effective treatment period.

The relationship between streptomycin resistance and dosage is a subject of considerable speculation, especially as it may pertain to intermittent administration of this antibiotic. It has been amply demonstrated that within limits the total daily dosage of streptomycin, as well as the frequency of daily injections in no way alter the time of occurrence or incidence of resistant organisms. One can conclude that a fairly constant exposure of tubercle bacilli to streptomycin results in the appearance of resistant forms. On the other hand, we are faced with the striking fact that the intermittent administration of streptomycin, at intervals of three, four, and five days, results in a prolongation of bacterial sensitivity.

In brief, experimental evidence favors two theoretical explanations of bacterial resistance: that of genetic selective mechanisms, and that of acquired characteristics. The former has received considerable support in explaining resistance in bacteria other than tubercle bacilli, but lacks sufficient evidence to explain streptomycin resistance in *M. tuberculosis*. The theory concerned with acquired characteristics implies that an entire population of tubercle bacilli can, in an almost simultaneous fashion, develop resistance to streptomycin without dependency on "variants." It is probable that both theories, working together, may eventually explain the development of resistance. In practical study, few test tube or animal experiments support either theory.

It is conceivable that the apparent prolongation of streptomycin sensitivity on intermittent dosages may in some way be related to the life cycle of the tubercle bacillus. In the test tube, this has been calculated by Youmans<sup>18</sup> to be between 36 and 72 hours. If this cycle is interrupted at the proper intervals, possibly every 72 hours, this interruption may result in serious alteration of the metabolic activity of tubercle bacilli so that they are incapable of the form of adaptation required to develop streptomycin resistance. On the other hand, if the organism is constantly exposed to streptomycin, it may in some manner adapt itself more rapidly to such exposure with subsequent resistant forms, such adaptation occurring through the forced necessity of altered growth and metabolic activity. As a working hypothesis, this concept is open to considerable challenge as it is based entirely on empiric observations and not on controlled experiments.

The mechanism of developed bacterial resistance is not understood; however, if current studies \* substantiate the observation that bacterial sensitivity is prolonged during the intermittent administration of streptomycin,

\* A study on the effect of intermittent dosage schedules is now in progress on a larger series of cases at Fitzsimons General Hospital.



a number of practical benefits will result. In view of the importance of "streptomycin protection" against bronchogenic spreads, the first advantage of prolonged bacterial sensitivity is manifested where collapse procedures are necessary. Because bacterial resistance develops rapidly, much emphasis recently has been placed on shortened treatment periods. Since roentgen-ray response to streptomycin therapy is not immediate, determinations of the feasibility of proposed surgical procedures or management during 30 to 42 days of treatment are difficult and frequently inaccurate; on the other hand, if initiation of collapse procedures is withheld pending manifestation of delayed resultant roentgen-ray changes, several months of possible therapeutic effect will be sacrificed and an actual exacerbation or spread of the disease might occur. Furthermore, the effect of a second course of streptomycin administered at this time as protection against bronchogenic spread might be lost if bacterial resistance has developed. Consequently, it seems logical to assume that the ideal management would consist of a continuation of the suppressive action of streptomycin until the time that an accurate evaluation and decision as to future management can be accomplished. In addition, with this prolonged continuous suppressive action of streptomycin, it is conceivable that in certain cases contemplated surgical procedures might be avoided or at least be rendered less radical.

Since antibiotic retreatment is seemingly ineffective in cases with resistant organisms, it is advantageous to maintain prolonged bacterial sensitivity for the management of post streptomycin exacerbations or spreads, because effective retreatment is then feasible. The following case history, included in this series, exemplifies effective retreatment of a patient with sensitive organisms.

#### CASE REPORT

A 29 year old white male entered Fitzsimons General Hospital on July 17, 1947, with a diagnosis of moderately advanced pulmonary tuberculosis, exudative in nature. Symptomatic onset of disease, characterized by gross hemoptysis, was on June 30, 1947. Gastric culture was positive for tubercle bacilli. He received streptomycin intramuscularly, two grams every fifth day, from August 30, 1947 to November 6, 1947, with excellent radiological results, as demonstrated by roentgenograms taken before and after treatment (figures 1 and 2). Sensitivity studies following treatment revealed streptomycin sensitive organisms. He subsequently developed an acute exacerbation of his disease (figure 3). At this time Wintrobe sedimentation rate increased from normal to 20 millimeters, sputum quantity was nil, there was no evidence of hemoptysis, temperature was normal, and there were no symptoms suggestive of an atypical or bacterial pneumonia. He was retreated with streptomycin from February 7, 1948 to April 29, 1948. A right pneumothorax was initiated on March 17, 1948, to maintain the excellent results obtained from the second course of streptomycin (figure 4). Since retreatment was initiated, sedimentation rate has again returned to normal, and repeated gastric cultures have been reported as negative.

The importance of successful retreatment is also emphasized in the management of cases where streptomycin is administered to afford symptomatic relief. If such symptoms recur with resistant organisms, further streptomycin therapy is probably ineffective and management is then extremely dif-

ficult. An effective streptomycin schedule which will not cause the development of bacterial resistance is highly desirable since the dissemination of streptomycin resistant organisms might be a public health disaster. By thus minimizing the incidence of streptomycin resistant organisms, future effectiveness of this antibiotic will not be subjected to the principle of diminishing returns.



FIG. 1. Chest roentgenogram before streptomycin therapy.

It is possible that hematogenously disseminated lesions, especially meningitis, might be treated more successfully if the effective treatment period could be prolonged with intermittent dosage schedules. The results on previous regimens generally have been unsatisfactory because of relapse and ultimate death with streptomycin resistant organisms.

With a marked decrease in the incidence of both bacterial resistance and streptomycin toxicity, much reluctance to treat primary and minimal tuberculous lesions with streptomycin might be obviated. Minimal lesions, as a rule, respond favorably to adequate conservative management, and the vast majority of primary tuberculous infections readily undergo regression and

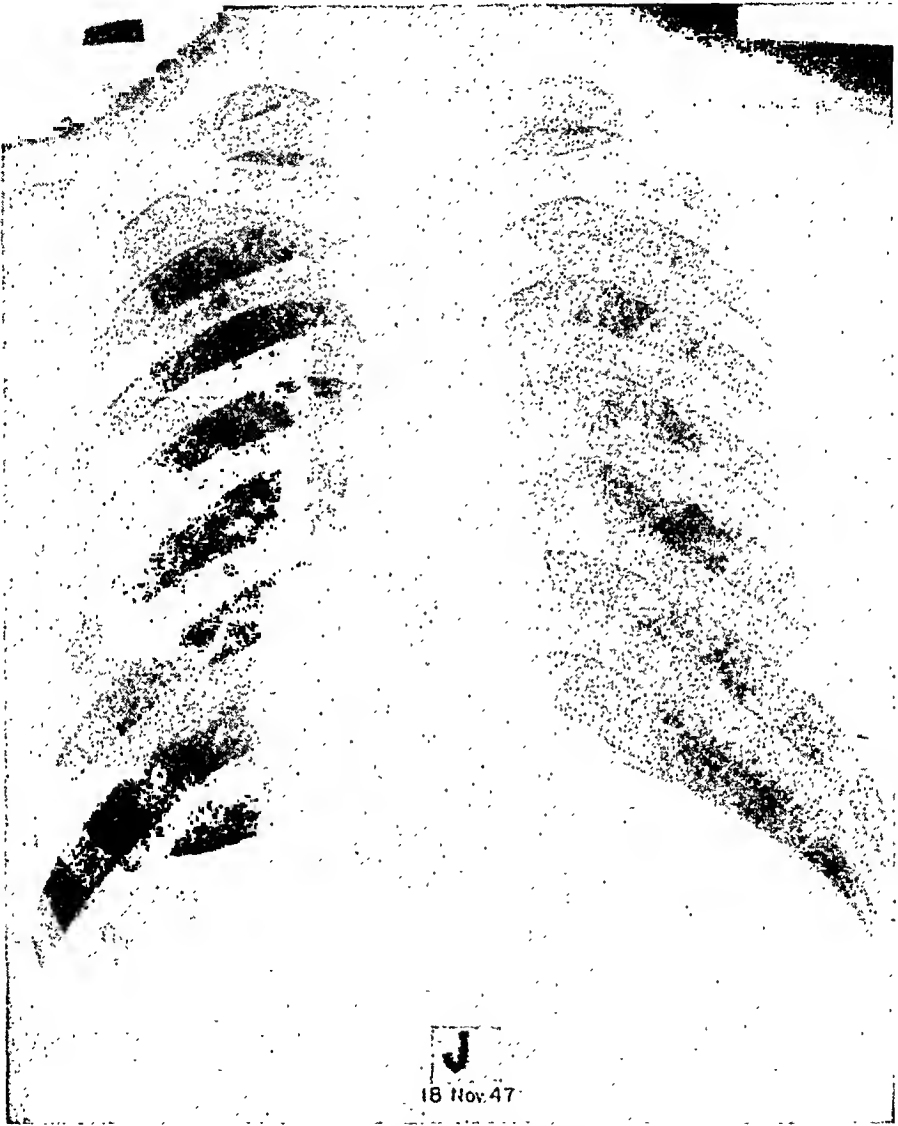


FIG. 2. Chest roentgenogram after streptomycin therapy.

healing. However, a certain percentage of these lesions, dependent on numerous factors, may progress by direct extension or hematogenous dissemination to lesions of grave prognosis. Consequently, protection against this hazard by an intermittent dosage administration of streptomycin appears possible and highly desirable.

In this study absence of subjective evidence of streptomycin toxicity, confirmed \* after treatment by normal caloric and galvanic vestibular stimulations in all but two cases,† suggests an additional advantage of the intermittent dosage schedules. In consideration of the previously decreased incidence of toxicity accomplished by reduced dosage, statistical significance of this observation in a small series of cases is questionable. However, in

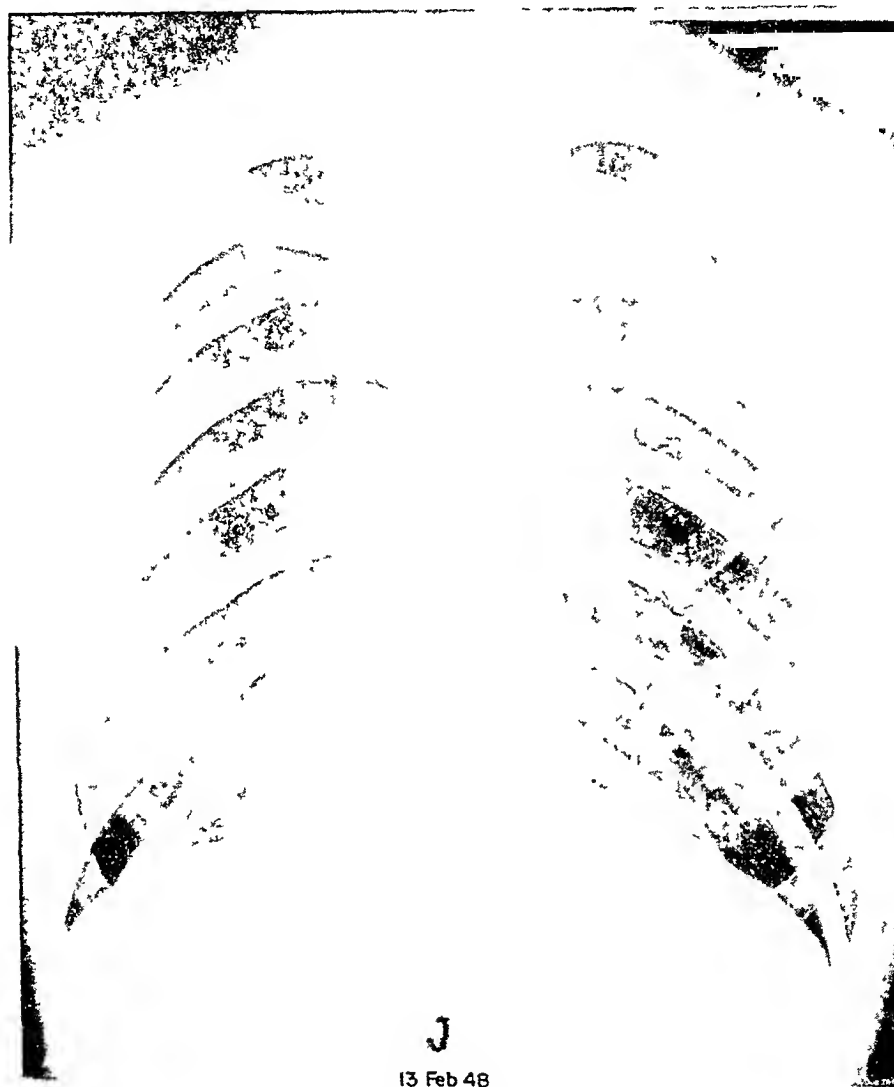


FIG. 3 Chest roentgenogram demonstrating post streptomycin exacerbation.

view of possible incurred disabilities and medicolegal aspects of streptomycin toxicity, any dosage schedule which might further reduce or even eliminate these factors, without sacrifice of therapeutic effect, merits consideration. Other advantages of intermittent dosage schedules, which are of real but

\* We wish to acknowledge our gratitude to 1st Lt Waymon B. Norman, M.C., A.U.S., who completed the vestibular function studies.

† Patients discharged from hospital before objective toxicity studies could be performed

secondary value, constitute reduction of cost and patient discomfort without relinquishment of prolonged therapeutic benefits.

If alternate dosage schedules are in some way responsible for the prolongation of bacterial sensitivity and further reduction of toxicity, the experimental results of suggested basic and clinical research ultimately may overshadow the practical values which we have enumerated. For the

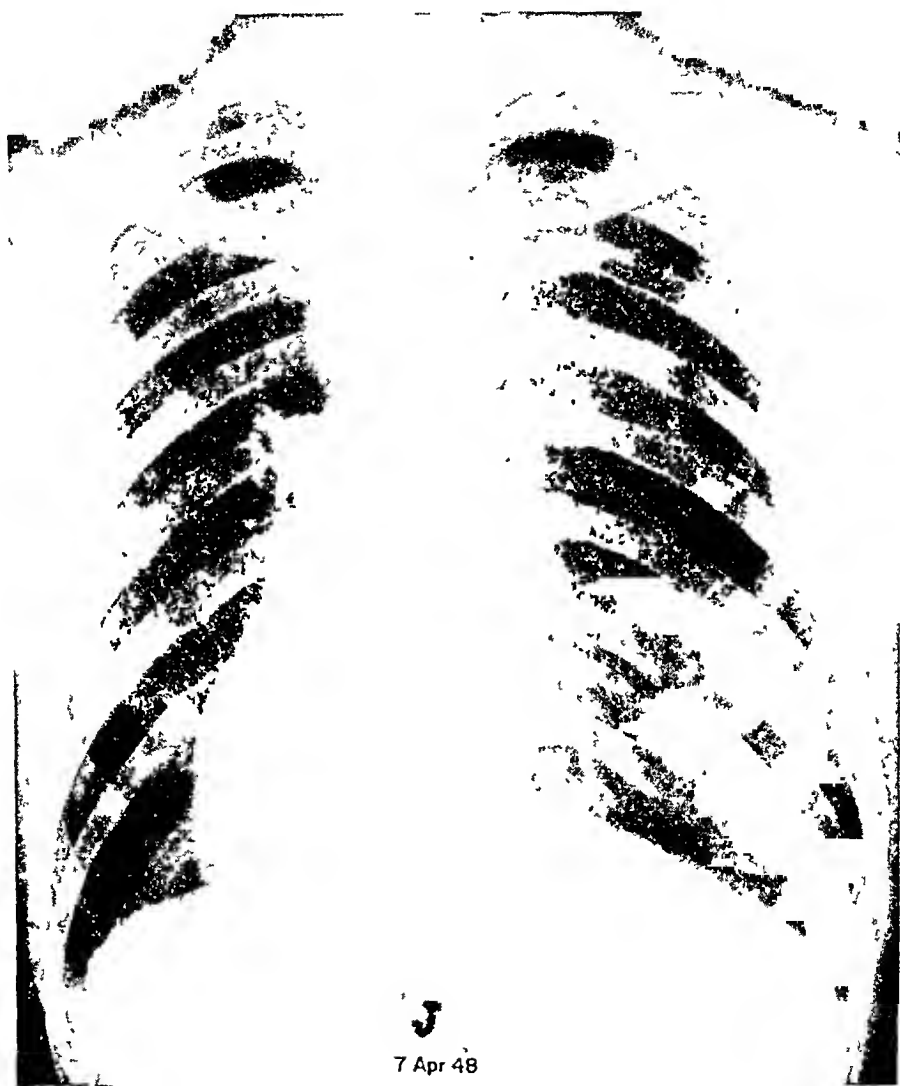


FIG. 4. Chest roentgenogram after retreatment with streptomycin. Right pneumothorax added after marked resolution had occurred.

moment, it would be important to determine: (1) the longest interval between streptomycin injections compatible with a sustained retardant action on *M. tuberculosis*, (2) the daily dosage, (3) the effects of sulfones and other antituberculous agents which could be readily combined with streptomycin intermittent dosage schedules and (4) how long sensitivity can be preserved under this plan of treatment.

## SUMMARY

The results of animal experiments suggested intermittent dosage schedules, and the results from 16 patients with pulmonary tuberculosis treated by this method indicate that sensitivity of *M. tuberculosis* can be prolonged. Thus the effective treatment period might be extended while expense and discomfort of administration can be reduced. In addition, it may be a method of further reducing toxicity. Intermittent dosage schedules suggest numerous experiments, both basic and clinical.

The greatest advantage of this plan is a prolongation of sensitivity suggestive of the following benefits:

- (1) Retreatment is more feasible.
- (2) Surgical procedures can be correlated with delayed roentgen-ray changes without sacrificing sensitivity.
- (3) Symptomatic treatment may become more widely used.
- (4) The incidence of resistant organisms in the general population may be reduced.
- (5) A more feasible plan for treating tuberculous meningitis is postulated.
- (6) Some hesitance in the treatment of minimal tuberculous lesions might be eliminated.

## CONCLUSIONS

1. In this series, clinical and roentgenological results are comparable with those obtained in previous one and two gram dosage schedules.
2. Subjective evidence of toxic reactions to streptomycin was not found in a single case of this series.
3. The sensitivity of the isolated tubercle bacillus to streptomycin in this series was prolonged.
4. Results of this study indicate further investigation of intermittent dosage schedules.

## ADDENDUM

A follow-up study consisting of 100 patients, divided into two groups receiving one and two grams of streptomycin every third day, respectively, is currently under investigation.

Clinical and roentgenological results obtained on these patients appear comparable to those obtained on other dosage regimens. Streptomycin toxicity was noted in only one patient, an 80 pound 53 year old white male, receiving two grams of streptomycin every third day. This patient exhibited mild transient vestibular dysfunction on about the one-hundredth day of treatment. His vestibular function returned to normal, however, following completion of 126 days of streptomycin therapy.

Though sensitivity studies on the entire series are incomplete, results to date appear to confirm the impression that bacterial sensitivity is prolonged. A comparison of results of sensitivity studies from this series with those obtained from an excellent bacteriological study on 45 patients who received one gram of streptomycin daily for 120 days<sup>21</sup> is presented in the following chart.

Since this study is incomplete, the above figures only represent results to date and are subject to modification as further sensitivity results are received.

Dosage Regimens	After 42 Days Treatment			After 70 Days Treatment		
	Total Pos. Cultures	No. Cultures Resis. to 10 MCM of Strep. per ML of Media	Per Cent Resis.	Total Pos. Cultures	No. Cultures Resis. to 10 MCM of Strep. per ML of Media	Per Cent Resis.
One gram per day	34	10	29	31	23	74
Intermittent regimens	38	0	0	28	4	14

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# RECENT ADVANCES IN THE STUDY OF ARTERIOSCLEROSIS \*

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PROGRESS in this most important and common of diseases continues to be disappointingly slow. Probably the exigencies of war have retarded research into the tantalizing problem of arterial disease. On the other hand there is increasing awareness of the aging of our population, and of the increasing number of deaths among young and old due to arteriosclerosis.

Some of the more interesting and important developments in the past two or three years will be discussed here. No attempt is made to cover the complete literature, but emphasis will be given to work which the author believes to be of significance. Four excellent reviews <sup>1, 2, 3, 4</sup> and two monographs <sup>5, 6</sup> have summarized work up to 1945. Moschcowitz <sup>7</sup> continues to express his fatalistic views on arteriosclerosis, saying it is the inevitable destiny of mankind. The nature of its pathogenesis and the possibility of its control still continue, however, to intrigue many investigators.

## CLINICAL FEATURES

The relation of the nutritional status and obesity to arteriosclerosis was carefully studied by four groups of investigators. Wilens <sup>8</sup> using autopsy material from Bellevue Hospital found advanced atherosclerosis about twice as common in the obese as in the poorly nourished group. The relation between the state of nutrition at necropsy and the degree of atherosclerosis was independent of age, sex, and the presence of hypertension or diabetes. Furthermore, obesity appears to be a more striking factor in the development of atheromatous lesions in men than in women and especially in coronary artery disease. Since the findings were postmortem material there is evidence that if the analyses were based on the probable state of nutrition prior to the final illness, the relationship would be even more striking. Of course, obesity alone is not the *cause* of atherosclerosis. For example, obese women have less atherosclerosis than obese men, and almost 40 per cent of poorly nourished people over 75 years of age have severe atherosclerosis at autopsy. As high as 15 per cent of all poorly nourished nonhypertensives over 35 years of age were found to have severe atherosclerosis. But the close correlation between the degree of obesity and the extent of the atherosclerotic process is evident from this survey.

Further evidence is contained in a study by Levy et al. <sup>9</sup> based on 22,000 Army officers. They found that the overweight group showed higher rates for later sustained hypertension. Adlersberg, Coler and Laval <sup>10</sup> studied the

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effect of weight reduction on arterial tension. Three-fourths of the patients who lost weight (an average loss of 23 pounds in eight months) had a reduction in blood pressure. French and Dock<sup>11</sup> found obesity present in 91 per cent of their 80 cases of fatal coronary arteriosclerosis in soldiers under 36 years of age.

Held<sup>12</sup> has suggested that when an arteriosclerotic lesion, even minute, develops in "any one of the centers regulating blood pressure, hypertension is the direct outcome." These centers are said to be the carotid sinus, the wall of the aorta, the medulla oblongata, the midbrain and splanchnic region.

We have used the words athero- and arteriosclerosis loosely, chiefly because these are the words used by the authors. Wolffe<sup>13</sup> has tried to differentiate the two. He considers atheromatosis a disturbance of lipid metabolism, perhaps due to a deficiency of an, as yet, unknown secretion of the pancreas. Calcification, true hardening, is often more protective than destructive as the greatest degree of thrombosis and obliteration of the lumen is found in the non-calcified atheromatous arteries. Arteriosclerosis (soft-hardening) is an all inclusive term, both for the long softening phase of the disease as well as for the deposition of calcium.

Howell<sup>14</sup> clinically examined 341 older persons and divided them on the basis of palpably thickened arteries. He found a rough correlation between the age and hypertension and the degree of hardening and tortuosity of peripheral vessels. The presence of arcus senilis has been found to be often closely related to a fairly extensive disturbance in cholesterol metabolism, including young patients with coronary artery atherosclerosis and familial xanthomatosis.<sup>15</sup>

### THE CEREBRAL ARTERIES

Attempts to produce cerebral atherosclerosis in rabbits by means of a high cholesterol diet proved unsuccessful even after ligation of the carotid and jugular vessels. The changes that were found in the arteries were also found in the non-cholesterol fed controls and these changes were rightly attributed to a hypertensive effect.<sup>16</sup> However, other work<sup>17</sup> showed that foam cells developed in one-third of cholesterol fed rabbits in the vascular tissue of the choroid plexus and in the suprachiasmatic capillaries. But atheromatous disease such as is seen in humans has not been produced.

Riese<sup>18</sup> studied 18 brains of patients over 77 years old. Practically all showed at least some degree of cortical atrophy, diffuse or localized. The degree of atrophy was not closely related to the age or to the clinical history. There were no special, pathognomonic or characteristic abnormalities found in the cortex of these old brains.

Grossly seen circumscribed areas of complete deficiency in the muscular coat was frequently found in the larger cerebral arteries.<sup>19</sup> The causes, it is said, may be due to either defective development of the wall, or degeneration and fibrosis of the intima, or perhaps the effect of an advanced atheroma.

Similar lesions in the internal elastic membrane are said perhaps to result in focal erosion or atheromatous degeneration.

Pollak<sup>20</sup> reports that one quarter of 2000 patients who came to autopsy at a state hospital were clinically diagnosed as having psychosis with cerebral arteriosclerosis. But only one quarter of these patients died primarily of arteriosclerosis. The majority died of pulmonary diseases.

Two types of venous changes in cerebral vessels were found in a series of 65 cases of hypertension and cerebral hemorrhage.<sup>21</sup> These were (a) reversible, with venous congestion, stasis and distention, and (b) structural changes in the vessel wall with extreme atrophy, degeneration and necrosis.

A group of 53 senile patients with cerebral arteriosclerosis or senile psychosis were studied by Liberson and Sequin.<sup>22</sup> They found that patients whose major symptoms were confusion and marked irritability had a much higher incidence of abnormal electroencephalograms than those whose symptoms were anxiety or delusions. However, often no EEG abnormalities were found in patients with anxiety, agitation and delusions.

A valuable technic for the visualization of cerebrovascular lesions has been described.<sup>23, 24</sup> Thorium oxide is injected into the internal carotid artery. This technic permits the roentgen visualization of that artery as well as the middle and anterior cerebral arteries and some of their branches. Incidentally, intracranial aneurysms were found in 0.5 to 1.6 per cent of cases on routine postmortem examination.<sup>23</sup>

To explain the mechanisms of rupture of cerebral vessels, Turner<sup>25</sup> devised a model of glass and rubber tubing. The more tortuous the course the earlier the rupture of the rubber tube and the more frequently does the rupture occur at the distal fixed point.

### PSYCHOSOMATIC ASPECTS

Binger<sup>26</sup> reëmphasized the fact that an intense anxiety state often exists preceding a myocardial infarction. And he also suggests, as Dunbar has, that often the coronary occlusion personality type is a stubborn, self-willed man given to hard work, self-discipline and a compulsive devotion to finishing a task, driving himself to success. His criterion of success means at least equalling his superiors and surpassing and dominating others. Superficially he appears self-reliant and outgoing, but he dislikes sharing responsibilities and is given to brooding.

Barbara<sup>27</sup> describes a 33 year old man who developed an acute occlusion of a coronary artery. He had a neurotic drive "to become perfect, powerful and unique" in order to compensate for his sense of inferiority. These authors and others<sup>28</sup> do not imply a causal relationship between the occlusion and infarction and the personality difficulties. But knowledge of the type of person in whom such atheromatous vascular accidents tend to occur has perhaps prophylactic and prognostic value.

## CORONARY ATHEROSCLEROSIS

Two very significant studies have recently shed much light on this all too frequent disease.

Dock <sup>29</sup> carefully studied the coronary vessels of 24 infants who died at birth. He found that even at birth the coronary intima is unusually thick and that the male begins life "with about three times as much coronary intima as the female." This helps to explain the tendency of males to coronary atherosclerosis with occlusion and infarction and the susceptibility of the coronary vessels generally. Atherosclerosis clinically is more common and severe in the presence of hypertension and/or faulty cholesterol metabolism, but this does not explain the marked sex difference. Certainly, if most men have "masculine coronary intimas," then given one or more of the other poorly understood factors leading to the development of atherosclerosis, there will be a predilection for the development of these lesions in the coronary intima as compared to other arteries of similar size. There seems to be no question that familial difference in the incidence of coronary artery disease depends in part on the anatomical difference at birth as well as the rate of thickening in determining the site and time of an atheromatous occlusion. In short there is a predilection of atherosclerosis for the epicardial branches of the coronary arteries based on the physiological relative thickness of the intima, which is greater in males than females, even at birth.

The second important contribution deals with the thrombotic phase of coronary thrombosis. Dicoumarol has been used in a number of series of cases. Reports are filtering into the literature all the time and it is too early critically to analyze the value of this treatment. Early reports by Nichol and Page,<sup>30</sup> Peters and associates<sup>31</sup> and Wright<sup>32</sup> among others led to a heightened interest in the blood clotting problem. Thus, Peters et al.<sup>31</sup> reported that the prothrombin clotting time was reduced in most cases of coronary thrombosis.

However, Cotlove and Vorzimer<sup>33</sup> found no alteration in whole or diluted plasma prothrombin time in patients with coronary occlusion with or without mural thrombosis. In fact, they found no change in the presence of digitalis, bed rest or ambulation or congestive heart failure. Furthermore, four out of eight cardiac patients who developed thrombophlebitis or thromboembolism had no alteration in prothrombin time. Similar findings have been reported by Meyers and Poindexter.<sup>34</sup>

On the other hand some evidence has been found<sup>35</sup> that many lesions classified as atherosclerosis are really mural thrombi which through organization have been transformed into fibrous intimal thickenings.

Falk<sup>36</sup> has reviewed the recent work in dicoumarol therapy for acute coronary thrombosis and the interested reader is referred to that paper as well as to the others which may have appeared since then. While final evaluation of dicoumarol therapy as a routine measure in the treatment of

acute coronary artery disease cannot be made as yet, it certainly is a promising lead which will get further study.

The problem of the relation of effort to attacks of coronary occlusion and infarction has long been a vital and poorly understood one. Blumgart<sup>37</sup> found severe effort to be a precipitating factor in a "small but definite proportion of cases."

On the other hand, French and Dock<sup>11</sup> found that vigorous effort brought on a fatal attack in over 50 per cent of their young patients. The fatal attack began during sleep in only 10 per cent of the cases. We might enumerate a few of their interesting findings because they show the complexity of the problem of coronary atherosclerosis. For example, among the 80 young, presumably healthy soldiers who died in coronary attacks, coronary thrombosis was found in 36 per cent of the cases. A recent infarct was found in only 19 per cent of the hearts, yet all died as cases of clinically acute coronary artery disease. However, old scars were found in 59 per cent of the hearts. A number of soldiers had had previous episodes of chest pain. Finally, multiple arteriosclerotic plaques were found in 84 per cent of the men. Thus, even in this group of "normal" young men there were numerous signs of extensive atherosclerotic disease.

Two recent investigations of coronary arteriosclerosis using the injection of radio-opaque material have appeared.<sup>38,39</sup> In a series of 70 *unselected* adult hearts<sup>38</sup> coronary occlusion was found in 12. And among these 12 hearts there were 31 points of obstruction. The lack of strict correlation between occlusion and infarction, which had often been noted before, shows up well in these statistics. Thus in two out of five hearts with a recent occlusion there were no new infarcts, and in one out of four hearts with recent infarcts there was no recent occlusion. Essentially similar results were obtained in a study of 166 hearts.<sup>39</sup>

### AORTA

Flory<sup>40</sup> found arterial occlusions in small and medium sized vessels of the spleen, pancreas and in the kidneys, where they caused wedge-shaped areas of cortical atrophy. These seemed to be emboli from eroded atheromatous plaques of the aorta.

That tissue anoxia may play a rôle in the pathogenesis of arteriosclerosis is suggested by the investigation of Blumenthal<sup>11</sup> on 175 postmortem specimens of the ductus arteriosus. The pathological changes seen in the ducti are similar to those seen in arteriosclerotic lesions.

### PERIPHERAL VESSELS

Sympathectomy has been performed in an attempt to improve the circulation to the lower extremities in the presence of moderate or severe arteriosclerosis. Telford and Simmons<sup>12</sup> experience in 98 cases with symptoms of intermittent claudication was disappointing, while de Takats' et al.<sup>43</sup> study

of 25 patients was more encouraging. At any rate there is still no unanimous opinion as to the value of sympathectomy. Probably, as these authors indicate, there is a certain group of patients who will be benefited. Further study is needed to differentiate this group.

The effect of smoking on the peripheral blood flow continues to attract interest. Thus, Stewart and co-workers<sup>44</sup> found that the smoking of cigarettes does cause arteriolar constriction with diminished blood flow to the peripheral arteries in the older patient with arteriosclerosis, but this is quantitatively less than in young normal adults.

Weinroth and Herzstein<sup>45</sup> found a 20 per cent higher incidence of thrombosed peripheral arteries in smokers as compared to non-smokers in a group of 301 diabetics. They found no arteriosclerotic vascular disease in non-smokers under 40 years of age, whereas in smokers in the same age group the incidence was between 25 to 33 per cent. In another study<sup>46</sup> of 249 male diabetics these authors found clinical evidence of arteriosclerotic peripheral vascular disease in 51 per cent of cases. One quarter of those under 40 years old were afflicted. This further substantiates our knowledge of the selective and frequent premature arteriosclerosis in the lower extremities of diabetics.

Moenckeberg's sclerosis was clearly described by Silbert and Lippmann.<sup>47</sup> They emphasize its rarity (13 in 2600 cases of arteriosclerotic peripheral vascular disease). It is not a senile degenerative disease and quite different from the intimal disorder variety. It occurs in young and middle aged men, who show no sign of impaired circulation anywhere. Extensive peripheral calcification is found on roentgen-ray examination. The course is very benign and no treatment is needed.

Two interesting developments in therapy deserve mention. Katz<sup>48</sup> used ether intramuscularly and intravenously in cases of diabetic gangrene and peripheral arteriosclerosis. There was immediate relief of pain, as well as a lowering of the blood pressure and a diuresis. Relief from the pain of intermittent claudication often lasted for weeks or months. Similarly excellent results following parenteral administration of histidine and ascorbic acid in order to elaborate histamine *in vivo* have been reported.<sup>49</sup> If these reports can be substantiated then a definite addition to our inadequate therapeutic tools will have been made.

#### EXPERIMENTAL WORK: CHOLESTEROL

The process of unravelling the cholesterol-arteriosclerosis knot continues. A widespread misconception based on high cholesterol diet feeding experiments in rabbits is slowly being cleared up. There was a tendency in many quarters erroneously to associate the blood concentration of cholesterol with the total amount of fat in the body or with the rate of absorption and excretion. The serum level is merely a quantitative estimate of the amount of the lipid in transport at that moment.

That there are individual differences in the ability to metabolize cholesterol even in hypercholesteremic rabbits has been shown by Pollak.<sup>50</sup> And in children<sup>51</sup> the amount of cholesterol in the serum was independent of the intake.

Furthermore we must be careful in making clinical deductions from experiments on animals because in rabbits, the favorite for induced atherosclerosis experiments, the age and weight of the animal play a significant rôle in the final results.<sup>52</sup>

Popjak<sup>53</sup> found that the level of free cholesterol in the plasma regulates fat metabolism by determining the rate of mobilization of fatty acids from the depots and the rate of phospholipid synthesis. This has broad implications and further work along this line is indicated.

Recently a suggestion has been made<sup>54</sup> that there may be a protective value to cholesterol in some forms of arterial disease. Dogs on a high fat low protein diet developed arterial lesions resembling human periarteritis nodosa and rheumatic arteritis, if the kidneys were damaged. The dietary factor responsible was a heat stable lipid found in cod liver oil among other foods, but was not vitamin A or D. These lesions could be retarded by feeding cholesterol and vitamin E.

In connection with the latter, Bruger<sup>55</sup> reported that in cholesterol fed rabbits, parenteral vitamin E appreciably augments the deposition of cholesterol in the aorta and increases only slightly the concentration of cholesterol in whole blood and in the liver.

It has also been shown that rabbits on a high cholesterol diet with the addition of olive oil deposited more cholesterol in the liver and aorta than non oil-fed controls although serum levels were only slightly increased.<sup>56</sup> And on the other hand, rats fed egg yolk powder developed hypercholesterolemia but no aortic atherosclerosis.<sup>57</sup> These investigations are further examples of the dissociation between serum and tissue concentrations of cholesterol.

Hueper<sup>58</sup> continuing his important investigations has found that the colloids in the serum of dogs and rabbits on a high cholesterol diet were more labile, i.e. flocculated more easily when shaken with such "colloid-active" substances as thiocyanides, thiourea and isotonic saline solution. This vibratory lability, resembling the churning of butter, is partly dependent on the formation of a film in the foam at the air-liquid interface. He concludes that dogs fed cholesterol in oil show a definite increase in the ether extractable fraction of both total and esterified cholesterol, which is probably colloiddally less stable than the cholesterol fraction bound to proteins. The interested reader is referred to his exhaustive review<sup>2</sup> for a more complete picture of colloidal plasmatic disturbance.

Hueper has also used such substances as sodium cellulose glycollate<sup>59</sup> and hydroxyethylcellulose<sup>60</sup> to support his concept that "in the genesis of these changes the macromolecular colloidal matter present in plasma is taken up by endothelial cells, which are transformed into foam cells, and infiltrate

extracellularly into the subendothelial spaces in which normally a turbulence of the blood exists, and where thereby a vibratory lability of the plasma colloids is produced."

For many years thyroid extract and the iodides have been known to reduce the incidence of atherosclerotic lesions in certain cases under special conditions. In a recent report<sup>61</sup> potassium iodide protected three out of 16 and thyroid extract two out of 16 chickens fed a high cholesterol diet from developing atherosclerotic lesions.

However, thyroidectomized rabbits were not protected from atherosclerosis by adequate doses of potassium iodide.<sup>62</sup> The latter finding suggests that the protective action of the iodides is mediated through the action of iodine on the thyroid gland.

Calcium deposits have been studied by Frondel and Prien<sup>63</sup> who found that carbonate-apatite was the principal inorganic salt in pathological calcification. It was the principal salt in tuberculous lymph nodes and subcutaneous hematomas but was found in small amount in the concretions of sclerotic arteries.

The elastic tissue of the larger arteries was studied by Carlborg<sup>64</sup> who describes the "Grönblad-Strandberg syndrome." This is a disease of degeneration of the elastic tissue in the arterial wall. It is characterized by the occurrence of "typical eyeground angioid streaks with pseudoxanthoma elasticum." An abnormally low pulse wave velocity was cited as evidence of widespread elastic tissue damage. The elastic tissue of the aorta is believed to protect the left ventricle from hypertrophy and this tissue in the peripheral arteries acting as a shock absorber prevents the "wearing out of the arterial wall."

## CONCLUSION

Some of the more important recent developments in the study of arteriosclerosis have been reviewed. The advance is slow but progressive. Unfortunately a chronic almost ubiquitous disease does not attract as much interest among physicians and laymen as do the more spectacular infectious diseases. But the overwhelming importance socially as well as medically of this disease makes increasing investigative work imperative. The next decade should see great advances, at least as long as there are men who do not believe that arteriosclerosis and its sequelae are "the inevitable destiny of mankind."

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# CASE REPORTS

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## CARONAMIDE\* AND PENICILLIN IN SUBACUTE BACTERIAL ENDOCARDITIS DUE TO *STREPTOCOCCUS FAECALIS*†

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PENICILLIN is the antibiotic of choice in the treatment of subacute bacterial endocarditis<sup>1</sup> if the organism is sensitive to the bactericidal action of penicillin.

Adequate daily dosage of penicillin over a sufficiently long period is imperative in obtaining clinical success with antibiotic therapy.<sup>2</sup> Insufficient amounts of penicillin may produce a deceptive response, with disappearance of symptoms, drop in temperature and sterile blood cultures, but as soon as such inadequate treatment is discontinued bacteremia promptly returns.<sup>3</sup> Another danger inherent in sub-curative therapy is the development of resistance to the antibiotic by the pathogenic organism. Subsequent therapy may require extremely large daily doses of penicillin.<sup>4</sup>

Definition of the term, "adequate daily dosage," is exceedingly difficult, and in our present state of knowledge appears to be directly related to the strain sensitivity of the organism *in vitro*.<sup>5</sup> Bacteriological determination of the degree of resistance to penicillin, of the organism isolated from the patient's blood stream, is essential in determining adequate daily dosage of antibiotic. Hence, bacteriological identification and classification of the pathogen are of primary importance.<sup>6</sup> The effective daily dosage of penicillin may vary from 500,000 units to many millions of units, depending upon the type of organism, its antibiotic resistance, and the known or probable duration of the infection prior to the institution of antibiotic therapy.<sup>7</sup>

The period of time necessary for the continuous administration of penicillin to effect clinical arrest of the infection has been reported to vary from three weeks to 17 months,<sup>8</sup> and the total dose of antibiotic per patient may range from 50 million units to 210 million units, or more. However, the total dose per se is relatively unimportant, since the continuous daily dose must be sufficient to provide plasma levels of antibiotic high enough to exert antibacterial action at all times during therapy. If the concentration of penicillin in the plasma is inadequate as far as antibiotic action is concerned, then the organism will continue to multiply, even during the administration of penicillin, and at one and the same time develop increased antibiotic resistance *in vitro* as well as *in vivo*.<sup>6</sup>

\* Staticin' caronamide was supplied through the courtesy of Sharp & Dohme, Inc., Philadelphia, Pa.

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The use of anticoagulants in combination with antibacterial agents in the treatment of subacute bacterial endocarditis<sup>9</sup> has not been supported by statistical, anatomical or histological evidence,<sup>10</sup> thus indicating that anticoagulants are not a necessary adjunct to therapy of this disease with penicillin.<sup>11</sup>

Penicillin alone may be administered by intermittent intramuscular injections, by continuous intramuscular or intravenous infusion-drip, or by one or two daily intramuscular deposits of massive doses of antibiotic in oil and beeswax.<sup>8</sup> The aim of any method is to maintain the highest penicillin blood levels for the longest period of time.<sup>12</sup>

This problem of maintaining very high penicillin blood levels where the infection is due to extremely resistant organisms, has been attacked from many angles, but its solution has remained difficult because of the very rapid and constant excretion of penicillin from the blood stream into the urine. Temporary inhibition of the renal tubular excretion of antibiotic by the use of diodrast,<sup>13</sup> by para-aminohippurate,<sup>14</sup> or by benzoic acid<sup>15</sup> has been successful in raising the level of penicillin in the plasma<sup>16, 17</sup>; but for a number of reasons, such measures do not lend themselves to practical therapeutic application. Both diodrast and para-aminohippurate must be given in very large amounts by constant intravenous drip, in order to saturate the tubular excretory mechanism. Benzoic acid will enhance antibiotic blood levels only when fluids and salt intake are restricted.<sup>18</sup>

A new concept of the competitive inhibition of the renal tubular excretion of penicillin<sup>19</sup> is based on the fact that glomerular filtration accounts for approximately 20 per cent of the penicillin appearing in the urine, while the remaining 80 per cent of urinary penicillin is excreted by the renal tubules.<sup>20</sup>

It has been shown that a new compound, caronamide,<sup>21</sup> can specifically and reversibly inhibit the renal tubular transport of penicillin. It is believed that caronamide has a specific, selective and reversible affinity for the enzyme transport mechanism responsible for the tubular excretion of penicillin from the plasma into the urine. By temporary inhibition of this enzyme mechanism, urinary penicillin is reduced to glomerular filtration.<sup>22</sup>

Extensive pharmacologic<sup>23</sup> and preliminary clinical investigation<sup>24</sup> of this new compound, 4'-carboxyphenylmethanesulfonanilide, have demonstrated that caronamide has an order of toxicity comparable to other drugs in common use,<sup>25</sup> and appears to have a wide margin of safety. In adequate oral dosage, caronamide will elevate the plasma concentration of penicillin at least fourfold.<sup>22, 24, 25, 26, 31</sup> This new drug should therefore be of definite clinical value when administered concomitantly with penicillin in the therapy of resistant disease conditions requiring high penicillin plasma levels.

Caronamide has been successfully employed as an adjunct to penicillin therapy in the treatment of subacute bacterial endocarditis.<sup>27, 30</sup> Accordingly, the co-administration of caronamide and penicillin was evaluated in a patient critically ill with a blood stream infection which had previously failed to respond to antibiotic therapy. The offending organism isolated from the blood stream was a resistant type of *Streptococcus faecalis*. Gratifying therapeutic response was obtained in this patient when sufficiently high plasma levels of penicillin were maintained for 36 days. The patient received 228 million units of penicillin, and ingested 1584 gm. of caronamide over a period of 66 consecutive days, with no untoward effect, as shown in the following case report.

## CASE REPORT

A married, colored woman, aged 25 years, was admitted to the Hospital of the Woman's Medical College on May 8, 1947, and delivered of a full-term male infant the next day. She was returned to her home, by ambulance, on the third postpartum day.

The patient was re-admitted May 16, 1947 to the Medical Service, complaining of headache, chills and fever of 48 hours' duration.

The past history revealed scarlet fever at six years of age, and an attack of acute rheumatic fever at 12, at which time she was hospitalized for three months. Residual valvulitis was apparent as mitral stenosis and insufficiency. There were no signs of cardiac distress during her recent (first) pregnancy.

At re-admission on the seventh postpartum day, the lochia was scanty and malodorous. Culture of cervical discharge revealed a profuse growth of  $\beta$ -hemolytic streptococcus, Group "D," and identical organisms were repeatedly isolated by blood culture. Cervical smear was negative for *Neisseria* and monilia.

In view of the previous damage to her mitral valve, and in the presence of positive blood cultures, a diagnosis of subacute bacterial endocarditis due to *Streptococcus faecalis* was made.

The laboratory reported this organism to be "sensitive" to penicillin (unitage not determined) and antibiotic therapy was instituted immediately. The patient received one million units of aqueous penicillin daily in divided doses by intramuscular injection for 11 days without therapeutic effect. Indeed, during this rather short period the number of colonies, on blood culture, increased from 13 to 17 per cubic centimeter of venous blood.

It was then determined that the organisms were resistant to penicillin in vitro, but sensitive to streptomycin. Accordingly, the administration of penicillin was discontinued in favor of streptomycin 4.0 gm. per day. This produced a prompt therapeutic response with rapid sterilization of the blood stream and negative cervical cultures. The patient's temperature and pulse rate, which had averaged 101.2° and 120 per minute, respectively, during the first two weeks of hospitalization, rapidly returned to normal limits and the patient looked and felt well. Because of lack of funds to purchase additional antibiotic, the administration of streptomycin was stopped after 10 days of continuous therapy.

The patient remained asymptomatic for only one week. Then her symptoms returned and her blood culture again was found positive for *Streptococcus faecalis* and she appeared very ill, with signs of septicemia and pericarditis. The organism isolated by blood culture was reported resistant in vitro to 0.6 unit of penicillin per cubic centimeter, but susceptible to 1.25 units per cubic centimeter.

Therapy with penicillin was resumed, and the patient received 150,000 units intramuscularly every three hours. On the third day a series of blood samples was withdrawn to determine the antibiotic plasma levels one-half hour, one, two, and three hours following the intramuscular injection of aqueous penicillin. These levels are presented as a "curve" (A-A) in figure 1.

The patient was then given 3.0 gm. of caronamide by mouth every three hours, concomitantly with 150,000 units of penicillin by the intramuscular route. She tolerated this new medication very well and exhibited a satisfactory clinical and laboratory response to this combined therapy. The blood culture was rendered sterile, whereas on a daily dose of 1,200,000 units of penicillin alone, culture of the blood produced from 10 to 13 organisms per cubic centimeter. Plasma levels of antibiotic were determined during the co-administration of caronamide and penicillin (curve B-B, figure 1), and compared with plasma levels obtained when identical amounts of penicillin alone were administered (curve A-A, figure 1).

Because of the high plasma concentration of antibiotic obtained in the presence

of caronamide, it was decided to reduce the daily dosage of penicillin but maintain the intake of oral caronamide at 24.0 gm. per day. This procedure verified an anticipated response, namely, a recrudescence of her disease with positive blood cultures. The resistance of the organism had increased further to 1.25 units of penicillin per cubic centimeter of broth culture and now required 2.5 units of penicillin to inhibit *in vitro* growth.

**Enhancing Effect of 3 Grams Oral Caronamide when given  
Concomitantly with Aqueous Penicillin  
by Intramuscular Injection,  
150,000 Units every 3 Hours**

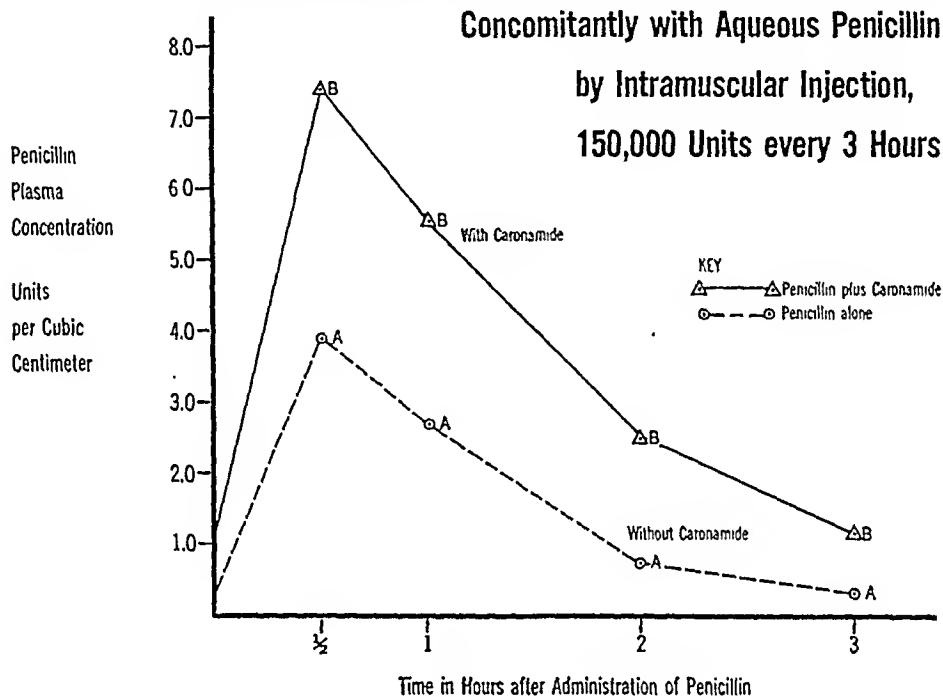


FIG. 1.

The dosage of penicillin was gradually increased (as shown in the chart), and it was found that 4 million units of antibiotic daily, plus 24.0 gm. of caronamide, were required to sterilize the patient's blood stream. The enhancement of antibiotic plasma levels with caronamide, while the patient received 4 million units of penicillin daily, is shown graphically in figure 2.

This combined therapeutics was continued for 66 consecutive days without toxic manifestations. The patient exhibited a prompt clinical response, and on the sixth day presented a negative blood culture. She remained asymptomatic during the remainder of her hospital residence and was discharged, disease "apparently arrested," on October 11, 1947.

Although the time interval is too short to establish a follow-up study in this case,\* it might be stated that on adequate dosage of penicillin plus conjoint administration of 4'-carboxyphenylmethanesulfonanilide, 10 consecutive blood cultures at three-day intervals were negative during the phase of combined therapy, and these were followed by six additional blood cultures, at weekly intervals, all of which were consistently negative following cessation of all antibiotic therapy.

\* Patient reported well and active 18 months later.

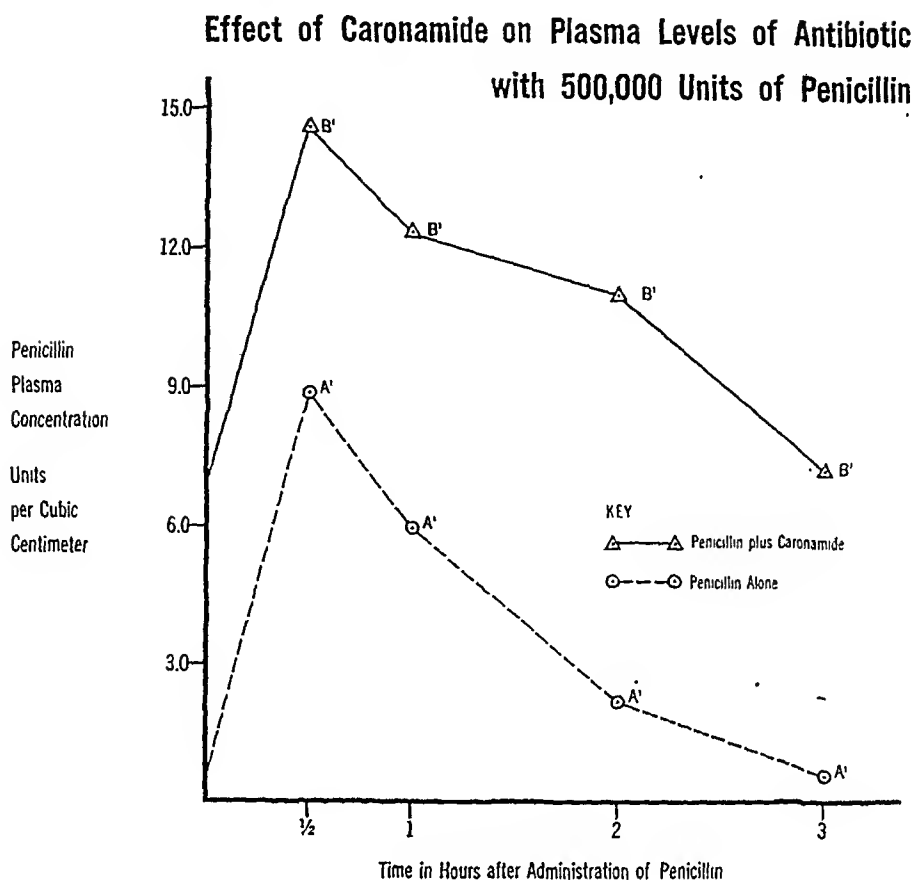


FIG. 2.

## COMMENT

It may be of interest to comment briefly on some additional laboratory findings in this patient.

During the period of caronamide administration mentioned above, blood samples were withdrawn on three different days to determine caronamide concentration in the plasma by means of a colorimetric method described by Ziegler and Sprague.<sup>28</sup> Samples were obtained one-half hour, one hour, two hours and three hours following the ingestion of 3.0 gm. of caronamide at intervals of three hours. The last blood sample was withdrawn just prior to the next oral administration of the compound. The average of these determinations is presented in figure 3, which demonstrates a blood level of caronamide capable of inhibiting the tubular excretion of penicillin. It has been shown that 15 mg. of caronamide per cubic centimeter of plasma is the "critical level" of blood concentration of this compound. The desirable level of caronamide ranges from 20 mg. per cent to 40 mg. per cent, for therapeutic enhancement of penicillin plasma levels.<sup>29</sup>

During the entire course of adjuvant antibiotic therapy, routine blood counts and urinalyses were made. The erythrocyte count fluctuated from 3,780,000 on admission, to 4,700,000 during caronamide administration. The white blood cells varied from 16,450 to 4,800. The differential counts at all times presented normal ratios. There was no evidence of leukopenia nor granulocytopenia. At no time were blood transfusions indicated.



Upon re-admission to hospital on May 16, 1947, the urine was grossly contaminated with erythrocytes and white blood cells from the lochia and endometritis. This responded satisfactorily to the administration of streptomycin but promptly recurred when this antibiotic was withdrawn. As soon as the dosage of penicillin was adjusted to 4 million units per day and 24.0 gm. of caronamide given concomitantly, the pelvic infection as well as the septicemia was overcome, and the urine specimens presented no further cellular elements, with the exception of a short period of normal menses early in August.

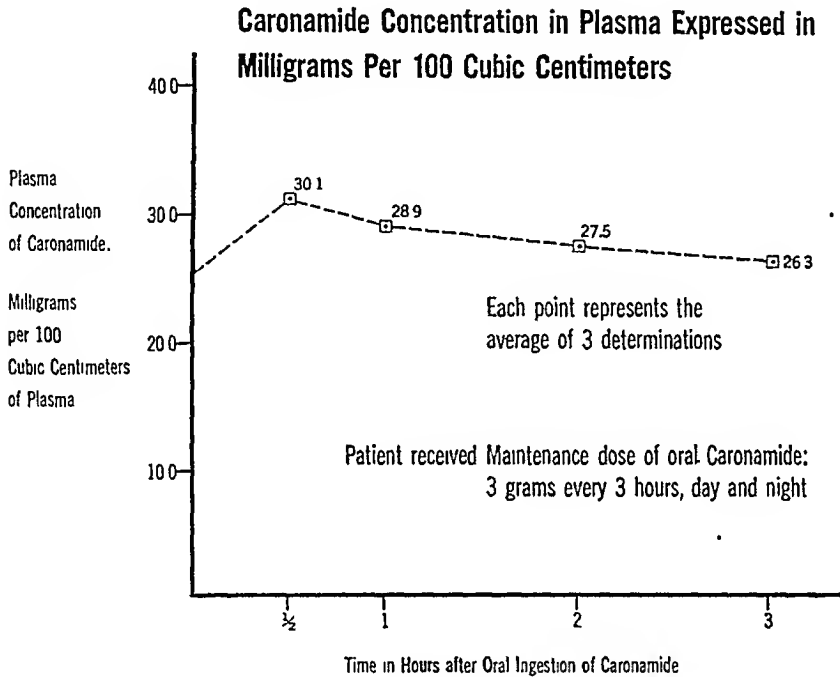


FIG. 3.

Frequently during the 66 consecutive days of caronamide administration (June 22 to August 27), the test for albuminuria was reported "positive," varying from a slight trace to coagulum, depending on the pH of the urine. It was found that when the pH of the specimen reached 6.0, caronamide would begin to precipitate, and that the more acid the urine (pH 5.5), the greater the degree of precipitation of the drug.

Routine tests for proteinuria require acidification, thus lowering the pH of the specimen, which in turn precipitates caronamide. Hence, a positive reading in the presence of urinary caronamide is an artefact and does not indicate albuminuria.

At no time, however, did this patient present evidence of crystalluria, nor were there signs of renal "block" or impairment, with the possible exception of the kidney function test. Just prior to the administration of caronamide, the phenolsulfonphthalein excretion was found to be 95 per cent in two hours. During exhibition of 4'-carboxyphenylmethanesulfonanilide the PSP test was reduced to 29 per cent. This is due to the fact that caronamide not only reversibly

### Showing Clinical Response to Coadministration

(S.B.E.: Strep. Faecalis)

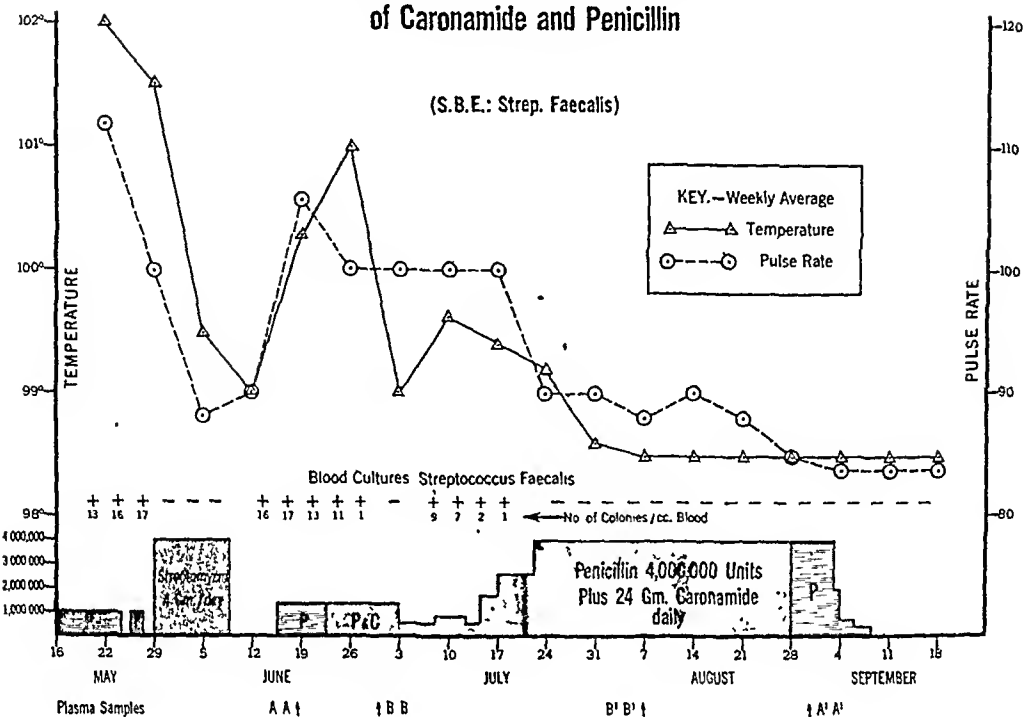


FIG. 4.

inhibits the tubular excretion of penicillin, but also inhibits the excretion of the dyes, phenolsulfonphthalein and diodrast, by the renal tubules. That the inhibition of PSP excretion is temporary (and reversible) is demonstrated, in this case at least, by prompt return of the renal function test to normal values shortly after withdrawal of caronamide. In addition, there was no increase in blood urea nitrogen, nor elevation of the blood pressure before, during or after this extensive "course" of penicillin-caronamide co-administration. The patient's blood was Type O, Rh positive. There was no change in bleeding time, coagulation time, prothrombin time, nor in erythrocyte fragility. During the entire course of her disease and its intensive therapy as reported herein, there was no icterus, dermatitis or drug fever; no involvement of the mucous membranes, no gastroenteritis and no impairment of the central or peripheral nervous systems. The sedimentation rate decreased to normal values as her infectious process was overcome.

## SUMMARY

A 25 year old colored female, with past history of scarlet fever and rheumatic fever in childhood, and resulting mitral stenosis, developed subacute bacterial endocarditis approximately seven days following delivery. The nidus of infection was apparently an endometritis. The offending organism was a resistant type of *Streptococcus faecalis* which was isolated upon culture of the lochia and from the patient's blood stream. The organism was resistant to 1 million units of penicillin daily, but responded promptly to 4.0 gm. of streptomycin per day.

One week following withdrawal of streptomycin, there was a recrudescence of infection as shown by repeatedly positive blood cultures. The organism was then found to have developed increased penicillin resistance.

This was overcome by the co-administration of oral caronamide (24.0 gm.) and intramuscular aqueous penicillin (4 million units per day). Blood samples were obtained at appropriate intervals during this therapeutic regimen to demonstrate the action of caronamide in enhancing the concentration of penicillin in the plasma when compared with plasma levels of antibiotic when equal doses of penicillin alone were administered. Caronamide plasma concentrations were also determined.

The mode of action of caronamide is presented elsewhere.<sup>10</sup> It is believed to be due to its specific, selective and reversible affinity for that enzyme substrate responsible for the renal tubular transport and excretion of penicillin.

Caronamide did not cause tubular epithelial damage nor renal impairment in the patient reported herein, who tolerated a daily dose of 24.0 gm. of the drug for 66 consecutive days. Adequate penicillin plasma levels during this period resulted in sterilization of the patient's blood stream and an apparent clinical arrest of her disease.

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## COLD HEMAGGLUTINATION IN PERIPHERAL VASCULAR DISEASE \*

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IN 1925 Seishiro Iwai and Nin Mei-Sai in Korea described a patient with Raynaud's phenomena in whom chilling of the blood serum caused agglutination of the red cells.<sup>1</sup> Since then there have been scattered reports of peripheral vascular disturbances in patients whose blood serum possessed this power of cold hemagglutination. The most recent review of the subject lists 18 such cases and adds a nineteenth.<sup>2</sup>

In 1943 Stats and Wassermann published an excellent comprehensive analysis of the experimental and clinical significance of cold hemagglutination,<sup>3</sup> and several other investigators have discussed this strange phenomenon in its specific connection with vascular disease.<sup>1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16</sup> The basic question is one of pathogenesis: Does cold hemagglutination cause or merely accompany certain instances of vascular stasis?

Our purpose is to discuss this issue in the light of divergent evidence and to describe an additional case in point.

Some of the facts which deserve attention are as follows:

Cold hemagglutination implies that when the patient's serum is chilled in a test tube it will agglutinate all types of human erythrocytes, and that this process is completely reversible by the restoration of body temperature.<sup>3</sup>

In at least 19 patients whose sera exhibit this property, exposure of the extremities to cold environments has repeatedly produced stigmata of vascular stasis. The symptoms and signs have varied, but the following have been observed: cyanosis, blanching, mottling of the skin, coldness, numbness, paresthesias, and gangrene.<sup>2</sup> Harris, Lewis, and Vaughan have quite properly pointed out that some of these patients have been inaccurately labeled Raynaud's disease.<sup>18</sup> This helpful clarification may not, however, be germane to the problem of whether or not cold hemagglutination causes vascular stasis, since the signs and symptoms mentioned have impoverished blood supply as a common denominator.

It has been amply demonstrated in a number of these cases that the clumping observed in the test tube actually occurs in vivo, and that it is produced by cold and dissipated by warmth. Capillary microscopy revealed vessels plugged by agglutinated red cells.<sup>1, 4, 6, 8, 9, 13</sup> It is obvious that such intravascular agglutination must lead to diminution in blood flow, and that when cold hemagglutination occurs in vivo it must at least be an aggravating factor in any observed vascular stasis.

Nevertheless all instances of cold hemagglutination are not accompanied by demonstrable changes in circulation,<sup>3, 19, 20, 21, 22, 23</sup> nor can this be entirely a matter of titer since Stats and Wassermann refer to an individual whose cold hemagglutination titer was 1:30,000 and in whom no signs of vascular stasis were observed.

Despite some claims to the contrary<sup>1, 4</sup> there can be little doubt that all

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cases of Raynaud's phenomenon are not caused, nor even accompanied by, cold hemagglutination.<sup>2, 24</sup>

Two individuals with peripheral vascular stasis induced by cold in whom cold hemagglutination was demonstrated have been benefited by theobromine, presumably because of the resultant vasodilation.<sup>10, 25</sup> On the other hand one such patient was not benefited by sympathectomy.<sup>6</sup> In another the disappearance of the vascular abnormalities and of the cold hemagglutination coincided.<sup>2</sup>

In brief it would seem that the presence of cold hemagglutination in certain individuals with cold-induced vascular stasis is more than coincidence. However, cold hemagglutination is not the sole factor responsible for the vascular symptoms. Certainly Raynaud's phenomena and allied conditions can occur in the absence of cold hemagglutination. Why some individuals whose serum possesses cold agglutinins do not exhibit vascular stasis is a mystery. It is hard to imagine intravascular clumping on a large scale without impairment of the blood flow. At least two possible explanations suggest themselves. One is that cold hemagglutination is sometimes demonstrable in the test tube when it does not occur in the body. Macfarlane describes an interesting patient in whom cold agglutinins were readily demonstrable in vitro only if the plasma or serum contained citrate or oxalate. The agglutination was completely inhibited by calcium chloride.<sup>22</sup> In other words cold hemagglutination occurred only under artificial circumstances, and it is possible that the conditions necessary to produce cold hemagglutination were never present in the patient. A second possibility is that individuals whose serum contains a cold agglutinin maintain a peripheral temperature sufficient to prevent the reaction by adequate vasodilation. This might account for the beneficial effects of theobromine therapy.

Further investigation is certainly necessary to explain these matters, but a growing body of observations on the coexistence of cold hemagglutination and peripheral vascular stasis supports the view that in a certain group of patients red cell clumping is at least partly responsible for the symptoms. It therefore seems important that all such cases should be reported. The mere factor of numbers may eventually remove all doubt as to the pathological significance of cold hemagglutination. For that reason we present the following case history:

#### CASE REPORT

A 19 year old single white soldier was admitted to an Army hospital on October 28, 1946 complaining of blueness of the hands, feet, and lips for the previous two weeks.

He had been exposed to cold weather many times in the past, although he had never been frostbitten, nor until the present illness had he suffered any ill effects from cold. Fourteen days before admission he was on his way overseas. It was a cold morning, and he was walking around the deck. A friend pointed out to him that his lips were blue. He had already noticed "a numb dead feeling" in the lips, tip of the nose, ear lobes, hands, and feet, but he had paid no particular attention to these symptoms. He went below where it was fairly warm and observed that the anatomical parts mentioned above were "blue." The numb feeling was so great that it was difficult for him to flex his hands and fingers. In about an hour the blueness was gradually replaced by a bright red color, and at the same time he felt a burning, "prickly" sensation in the areas that had been blue. In about two hours the skin returned to a normal color, and there was normal sensation. A similar

episode occurred on the following 14 mornings, and once or twice the same thing occurred at night when the air became chilly. In each case it required at least an hour of warming for the signs and symptoms to disappear. The patient was somewhat surprised by these occurrences because as a merchant seaman he had sailed the North Atlantic in the dead of winter without any untoward effects. He was an uncomplaining individual, however, and did not consult his Dispensary Surgeon until the morning of the twenty-eighth. On that morning he arose at 7 o'clock and noticed that his hands, feet, lips, nose, and ears were blue and numb. The Dispensary Surgeon sent the patient to the hospital. It was a rather cold day, and when he arrived at 2 o'clock that afternoon there was still marked cyanosis of the hands and feet, although the face had apparently become normal.

In all other respects the patient felt perfectly well. There were no stigmata of any psychiatric abnormalities and no history of ingestion of any drugs likely to produce cyanosis. He had never worked with a pneumatic drill or any similar mechanical device.

The patient had had a severe sore throat without sequelae the previous year. In childhood he had had whooping cough, measles, chickenpox, and "quinsy." He fractured his left ankle playing football in 1938. He remembered no other illnesses or injuries. He denied venereal disease by name and symptom.

His mother was 40 years old and in good health. His father was said to have died of silicosis at the age of 36. He had worked in a brick-making plant. One brother, aged 21, was entirely well. The only other sibling, a boy, had died two days after birth. There was no family history of peripheral vascular disease except that the father had had varicose veins of the legs.

The patient reported that for the previous year he had drunk less than two-fifths of whiskey a month. For several years, he had smoked a package of cigarettes a day.

*Physical Examination:* Height, 5 feet 7 inches. Usual weight, 155 lbs. Present weight, 146 lbs. Temperature, pulse and respirations, normal. Blood pressure, 140 mm. of mercury systolic and 80 mm. diastolic. The findings were entirely negative except as noted below:

Two hours after admission to the warm atmosphere of the hospital the skin was not remarkable except for the feet and hands. The toes of the left foot and the great toe of the right foot were a solid deep blue color and were very cold. On the dorsum of the interphalangeal joint of the second left toe there was a one-quarter centimeter spot of superficial skin gangrene, which healed completely during the following week. Elsewhere the feet and hands were reddened in a patchy distribution and gave the appearance of being swollen, although there was no demonstrable edema. On the dorsum of the hands and fingers there were a few small spots of cyanosis. In the course of the examination the cyanosis disappeared completely, and the rubeosis became more generalized in the hands and feet. There was marked sweating of both hands and feet. All peripheral pulses were of good quality and equal bilaterally, including the following: radial, ulnar, brachial, dorsalis pedis, and posterior tibial.

*Course:* On the day after admission in the morning the patient's fingernail beds were slightly cyanotic, and all the toes were deep blue. These signs disappeared in the course of an hour.

On October 30 the same cyanosis was observed in the morning, and there was some superficial peeling of the skin of the fingers. A basal metabolic rate by the Read-Barnett formula was determined from the following data: blood pressure, 115/80; pulse pressure, 35; heart rate, 64; age, 19 years. Basal metabolic rate, plus 1 per cent. On the same day it was noted that a red count was impossible to perform because of spontaneous agglutination of the patient's red cells at room temperature. Detailed data on the titer of cold agglutinins are listed below (table 1).

TABLE I

Titer of Cold Agglutinins by Tube Method at Different Temperatures

Date	Titer at 37 C.	Titer at 27 C.	Titer at 8 C.	Type of Cells	Patient's Serum	Control Serum
10/30/46	0	1:2	1:1792	Patient's (washed)	Inactivated	
11/1/46	0	1:2	1:1792	Patient's (washed)	Inactivated	
	0	1:2	1:1792	Patient's (washed)	Fresh	
	0	1:56	1:1792	Type O	Inactivated	
	0	1:2	1:1792	Type O	Fresh	
	0	0	0	Patient's (washed)		Inactivated
	0	0	0	Patient's (washed)		Fresh
	0	0	0	Type O		Inactivated
	0	0	0	Type O		Fresh
*11/4/46	0	1:2	1:3584	Patient's (washed)	Inactivated	
**11/8/46	0	1:2	1:896	Patient's (washed)	Inactivated	
***11/13/46	0	1:2	1:3584	Patient's (washed)	Inactivated	

\* After the patient's hand was immersed in iced water for 2 min.

\*\* After 2 injections of intravenous typhoid vaccine.

\*\*\* After 3 injections of intravenous typhoid vaccine.

On October 31 and November 1 the same color changes as described above occurred in the morning and disappeared in the course of an hour or two.

There was no change in this occurrence until November 5. During the night of the fourth and on all subsequent nights except one a chemical heat pad was applied to the foot of the patient's bed all night long. As long as this regimen was carried out, the patient's feet and hands were entirely normal at all times, except as noted below.

On November 4 at 10 a.m. the patient reclined on a bed in a room whose temperature was 10° C. with hands and feet exposed. He was wearing light pajamas. There were no abnormal colors or sensations. The right hand was immersed in a pan of water containing ice cubes up to the wrist. Water temperature was 7°. The experimenter's hand was similarly immersed and within a minute both the patient and the experimenter felt a severe gnawing pain in the region of the palmar arch. The patient alone, however, also experienced a similar pain in the tips of all digits. The pain was promptly relieved by removing the hand from the water at the end of two minutes. At that time the experimenter's hand was bright red, felt hot, and in the course of the next five minutes returned to a normal color. The patient's hand was dead white, almost like ivory, from the water-mark down, while the water-mark was outlined by a two centimeter cuff of rubeosis. At the same time the toes of both feet began to assume a mottled blue hue with patches of white, gray-blue, and purple, and this process gradually extended upward until it involved both feet in their entirety. The heels and toes were more uniformly cyanotic, while the intervening areas were more mottled. During the next five minutes the patient reported that his hand felt "very numb, like the blood isn't running," and the tips of the toes, especially the great right toe, felt the same. By 10:20 the cuff of rubeosis included most of the dorsum of the hand, while the palm and all of the fingers and thumbs except for the distal ends of the phalanges had changed to a cadaverous white, and the ends of the phalanges were a grayish-blue color. In the course of the next 20 minutes all of the white areas became cyanotic, the rubeosis gradually moved downward until it replaced the cyanosis, and at 10:45 the hands were normal. The subjective changes disappeared at 10:35. The feet underwent rubeosis and subsequently returned to normal color by 10:56. At numerous intervals during the experiment all peripheral pulses were felt and were found to be perfectly normal.



It was decided to inoculate the patient with killed typhoid organisms intravenously to see if the foreign protein response would alter the cold agglutinins. On November 5 at 10 a.m. one hundred million organisms were injected. At 10:30 the patient developed moderate malaise and chilly sensations. Both hands and feet to the wrists and ankles became dead white and then cyanotic. At that time the patient's temperature was 98.2° F. by mouth. By 11 o'clock the patient felt hot all over; his temperature was 100°, and the hands and feet were bright red with pulses palpable at all distal interphalangeal joints. The fever rose to 105° by 3 p.m. The temperature fell to normal spontaneously by 4:30 a.m. On November 7 the patient was entirely normal.

On November 8 the same procedure was carried out, and the same events ensued. In this case the temperature reached 105° at 12:15. It fell to normal by 6 p.m.

On November 9, 10, 11 the patient was entirely normal.

On November 12 the patient was emotionally upset about the prospect of more fever therapy. The anxiety, however, caused no visible changes in hands or feet. The same fever therapy procedure was again carried out. This time there were no objective changes in the limbs, although the patient complained of some numbness and "stiffness" in the fingers and toes during the chilly phase. The temperature rose to 101.5° and fell to normal by 5 p.m. Relative immunity had been developed, but the agglutinin titer had not changed.

On November 13 the patient was entirely normal.

On November 14 the hot water bottle was forgotten, and the toes underwent the same changes as previously described. The patient's subsequent course in the hospital was uneventful.

The patient did not smoke while in the hospital.

*Laboratory Data:* Red blood cell count was impossible by ordinary methods. After the pipette was placed in the incubator a short time, clumping disappeared, and the red blood cell count was 4.27 million. White blood cell count, 12,150. Differential white blood count: polymorphonuclear leukocytes, 59 per cent; juvenile cells, 3.5 per cent; eosinophiles, 0.5 per cent; basophiles, 1 per cent; lymphocytes, 29 per cent; monocytes, 6 per cent; Turk irritation cells, 1 per cent. Urinalysis: dark yellow; specific gravity, 1.034; pH, 5; albumin and sugar tests were negative. Sediment contained only an occasional white blood cell. Bence-Jones protein test, negative. Kahn test, negative. Plasma protein, 7.1 gm. per cent; albumin, 4.4 gm. per cent; globulin, 2.7 gm. per cent; albumin-globulin ratio, 1.63:1. Cephalin-cholesterol flocculation test, negative in 24 hours, 1 plus in 48 hours.

An oxalated specimen of the patient's blood was centrifuged. The plasma was removed and the cells were twice washed in 0.85 per cent saline. When a suspension of these cells in normal saline was made in a proportion of 2 per cent, no agglutination was noticed. However, when a drop of the saline suspension of cells was mixed with a drop of the patient's serum, gross agglutination was seen after five minutes at room temperature. Serial dilutions of the patient's serum in physiologic saline were made, ranging from a titer of 1:2 through 1:7168, after the patient's serum was inactivated by heating at 56° C. for 30 minutes. 0.2 c.c. of a 2 per cent suspension of the patient's own red blood cells was added to each tube. One rack of tubes was placed in the refrigerator at a temperature of 7° C. One was left at room temperature at 27° C., and one was incubated at 37° C. Results were read in 12 hours. Agglutination was found in the refrigerated specimens in all titers through 1:1792, and in the specimens left at room temperature in a titer of 1:2. The system left at body temperature failed to agglutinate. The rack which was originally in the refrigerator was rotated to the incubator, where the clumped cells promptly broke up, and the test became entirely negative. The racks which were left at room temperature and in the incubator were refrigerated, and it was found that the red cells

agglutinated in a titer of 1:1792. Subsequent cold agglutination experiments are listed in table 1.

Corrected sedimentation rates in millimeters per hour by the Wintrobe method were obtained as follows:

Temperature	Patient's Blood	Normal (Control Blood)
8° C.	10.0	0.4
27° C.	15.5	5.1
37° C.	21.6	7.1

Blood drawn from the patient during the ice water experiment behaved in the same way except that the cold agglutinin titer went up to 1:3584. Similar results were obtained with blood drawn when the patient had a temperature of 105° F., but the titer was 1:896. On November 13, however, after completion of the typhoid treatment, cold agglutinins were again demonstrated in a titer of 1:3584 (table 1).

### COMMENT

It will be noted that chilling of this patient's hand caused cyanosis of the feet. It is evident that hemagglutination alone was not the mechanism. It is quite possible, however, that reflex vasoconstriction produced chilling, and that chilling caused cold agglutination in the vessels of the feet.

One point of interest in this case is the fact that the sedimentation rate was directly proportional to the temperature. The converse has been claimed in similar patients<sup>2, 8, 13</sup>. Our data support the contention of Stats and Wasserman that even when cold hemagglutination is present the increased viscosity produced by chilling may retard the sedimentation rate.<sup>3</sup>

The etiology of the disease in this patient, as in many other such patients, remains obscure. Cold hemagglutination has been reported in a wide variety of diseases and in healthy individuals.<sup>3</sup>

The substance responsible for cold hemagglutination is apparently a gamma globulin, and no one has yet explained what causes it to appear.<sup>3</sup> It is well known that foreign protein reactions alter the gamma globulins,<sup>26</sup> and for that reason we wondered if the injection of killed typhoid organisms would interfere with the cold agglutination in our patient. Obviously no change occurred. Similar therapy has been disappointing in ordinary idiopathic Raynaud's disease.<sup>24</sup>

Regardless of the origin of cold hemagglutination, however, it may well be helpful to classify individuals with cold hemagglutination and cold-induced vascular stasis under one heading. Whether or not the cold agglutinin is a manifestation of a more basic disease, it is likely that it may per se be at least partly responsible for the production of its own peculiar symptoms, such as the ones illustrated by our patient.

### SUMMARY

1. A review of the literature suggests that in some individuals cold hemagglutination is at least partly responsible for the production of peripheral vascular stasis.

2. A patient with Raynaud's phenomenon and a high titer of cold hemagglutinins is described.

3. The patient's sedimentation rate was retarded by cold despite the agglutination.

4. Intravenous injection of killed typhoid organisms had no effect on the Raynaud's phenomena nor upon the cold hemagglutinin.

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## DYSPHAGIA AND MITRAL VALVE DEFORMITY \*

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DIFFICULTY in swallowing is an unusual complication of cardiovascular disease. It occurs, in approximate order of frequency, in cases of aortic aneurysm, pericarditis with effusion, congenital anomaly of the aortic arch and dilatation of the left auricle. Left auricular enlargement as a cause of dysphagia is particularly rare. Bloomfield, in surveying the literature back to 1927, found only two such cases (cases 1 and 4 of Rösler) with a possible additional report in an untranslated Czechoslovakian journal.<sup>1</sup> Two other cases not included in Bloomfield's paper were described by Nichols and Ostrum in 1932.<sup>2</sup> Subsequent to Bloomfield's report, Newton and Levine reported in 1942 on a patient in whom thoracic decompression was required to relieve dysphagia from auricular compression of the esophagus.<sup>3</sup> Tinney, Schmidt and Smith, in 1943, added another case.<sup>4</sup> Not counting our patient then, only seven cases of dysphagia due to left auricular enlargement have been described in the past 20 years. Conversely, of 150 successive cases esophagoscoped because of dysphagia, not one was found due to compression by the left auricle.<sup>5</sup>

Considering the frequency with which appreciable compression of the esophagus is encountered during fluoroscopic examinations in patients with mitral stenosis, it seems surprising that symptomatic impediment to swallowing is so rare. The elasticity of the normal esophagus, its relationship to non-rigid structures on either side, and its consequent motility, appear to be the protective factors which allow the esophagus to tolerate considerable encroachment by the left auricle without developing functional occlusion.

### CASE REPORT

A 55 year old Negro laborer was admitted to the hospital on July 16, 1946, with symptoms dating back to May 15. On that day, three days after exposure to inclement weather, he developed coryza, malaise, and non-productive cough, but continued to work. Within two weeks the cough grew worse. He became dyspneic on ordinary activity and increasingly orthopneic. During the latter half of June he developed a choking sensation at the lower third of the sternum, a feeling of inability "to get the food through to the stomach." This progressed to the point of frequent vomiting immediately after meals, and occasionally in the course of a meal; the vomitus was not

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From the Cardiovascular Section, Medical Service, Kennedy Veterans Administration Hospital.

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FIG. 2.

FIG. 1

FIG. 1. Film taken on date of transfer to Cardiovascular Service. Fluid and pulmonary congestion on right as well as left. Generalized heart enlargement, particularly of left ventricle.

FIG. 2. Left oblique view. Same date as figure 1. Elevated left main bronchus and markedly enlarged left ventricle.

sour. He lost weight and strength progressively and entered another hospital on June 29.

On admission there, left-sided pleural effusion was found. Initial thoracentesis yielded "only a few c.c. of fluid," the appearance of which was not described and from which no organisms were grown on culture. The white cell count was 9200 with normal differential; the patient was not septic; and repeated chest taps yielded sterile fluid. Nevertheless, treatment with both sulfonamides and penicillin was instituted, supplemented by penicillin in massive doses intrapleurally. The patient failed to improve; cough, dyspnea, and orthopnea persisted. Dysphagia and vomiting became progressively worse, and he was transferred, finally, as a case of empyema to the Surgical Service of Kennedy Veterans Hospital.

The past history was notable only for syphilis contracted in 1918 and untreated until its rediscovery during a pre-employment examination in March, 1946. Weekly arsenical and bismuth therapy was instituted then but was interrupted by the onset of the current illness. The patient had never had any other illness related etiologically to cardiovascular disease and had had no symptoms referable to his heart. Indeed, he had been well, hard-working, and symptom-free his entire life prior to the present illness.

Findings recorded on admission to the Surgical Service were: evidence of marked weight loss, low-grade fever, left pleural effusion, enlarged heart, and enlarged liver. The cachexia, protracted vomiting, dysphagia, and cough led to consideration of pulmonary tuberculosis, bronchogenic carcinoma, and obscure visceral malignancy as diagnostic possibilities. Bronchoscopy showed only displacement of carina to the right and narrowing of the left main bronchus. No evidence of tumor was seen. Comprehensive study of the genitourinary and gastrointestinal tracts failed to disclose neoplasm. A chest film showed a markedly widened heart shadow, hydropneumothorax on the left, and shift of the mediastinum to the right.

Study in the Cardiovascular Section revealed a cachectic man in advanced congestive heart failure, unable to retain food, markedly orthopneic, with engorged neck veins, bilateral pleural effusion and marked pulmonary congestion above the level of effusion on the right, a tender liver edge palpable four fingers'-breadth below the costal margin, and dependent edema. The left margin of the heart extended to the anterior axillary line in the sixth interspace. A sharp first sound at the apex was followed by a harsh, long, high-pitched systolic murmur occupying all of systole, and maximal over the mitral area.  $A_2$  and  $P_2$  were both moderately accentuated. A faint, low-pitched diastolic murmur was audible in the left lateral position. The rate was 100 and the regular sinus rhythm was interrupted by frequent extrasystoles. Blood pressure was 128 mm. Hg systolic and 92 mm. diastolic.

Fluoroscopy revealed an enormously enlarged heart with left ventricle and left auricle particularly prominent. In the right oblique view the left auricle bulged backward to occupy the entire width of the retrocardiac space. The middle third of the esophagus was compressed and markedly narrowed; there was definite hesitancy of the barium at the upper border of compression. Systolic pulsation of the left auricular outline could be seen with each ventricular contraction. In the left oblique the left main bronchus appeared elevated. The massive left pleural effusion pushed the mediastinum slightly to the right. The aortic shadow was not remarkable.

Electrocardiogram showed left axis deviation, shallow T-waves in the standard leads, low R in the right-sided chest leads, and frequent ventricular extrasystoles. Urinalysis and blood count were normal. Serology (Kahn) was repeatedly reported as doubtful.

On a régime of bed rest, salt restriction, rapid digitalization, and a single dose of a mercurial diuretic, the patient made remarkably rapid progress. Within 48 hours all cough and dyspnea had disappeared, venous pressure was down to normal, and the

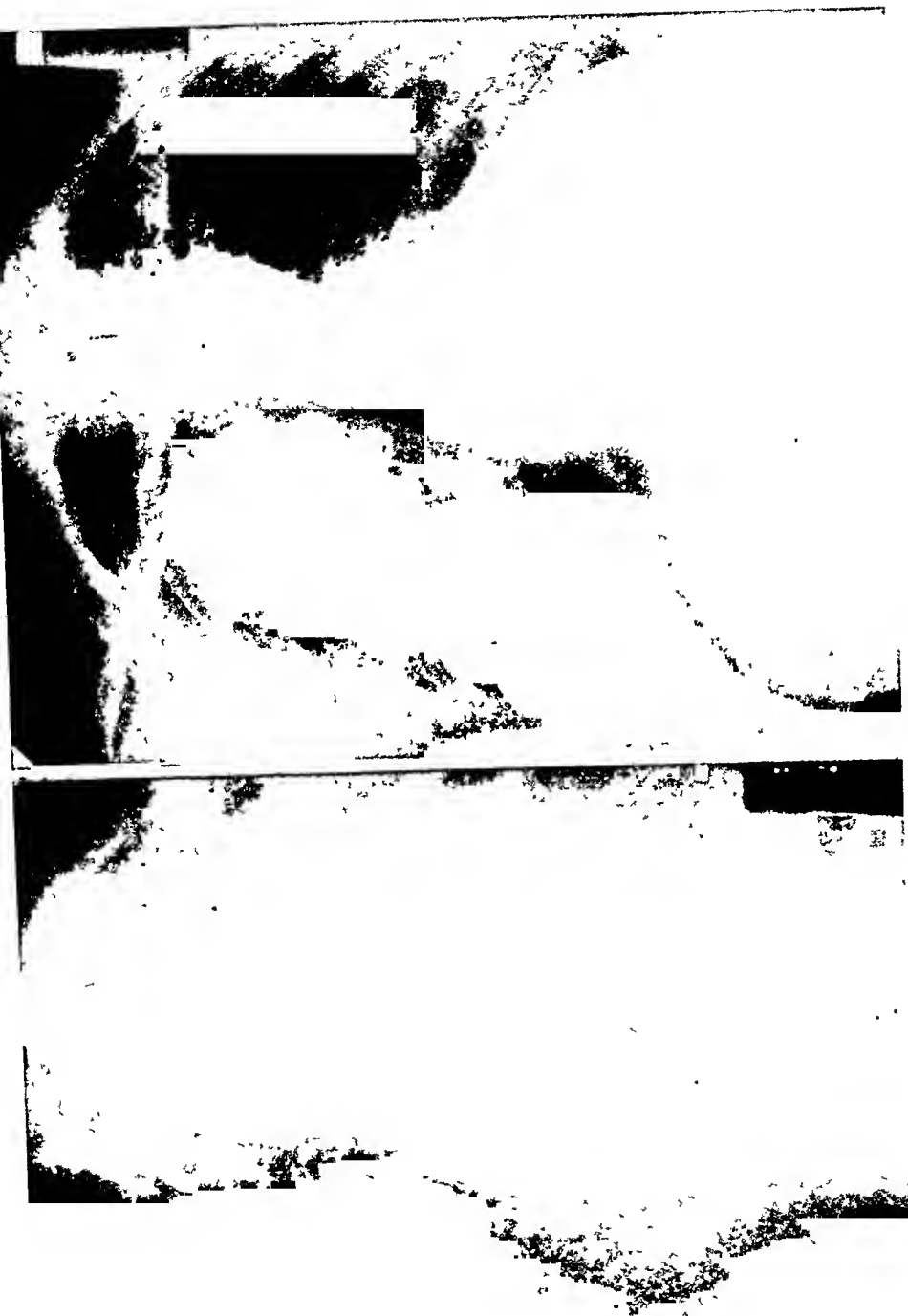


FIG. 3.

FIG. 3. Right anterior oblique taken shortly after admission showing compression of esophagus by enlarged left auricle. Fluoroscopy on date of transfer to Cardiovascular Service showed much more marked esophageal compression with only a trickle of barium passing the compressed area.

FIG. 4. A week after institution of treatment for failure. Marked reduction in size of left ventricle and left auricle. Retrocardiac space free.

FIG. 4.

liver could not be palpated. The right lung field was clear and dependent edema was gone. For the first time in months the patient was able to swallow freely and retain food. He gained 16 pounds in seven days. Reexamination under the fluoroscope a week after the beginning of treatment showed only residual pleural thickening on the left and an entirely clear lung field on the right. The esophagus was still displaced backward by a slightly enlarged left auricle, but the barium swallow was unimpeded and the retrocardiac space almost clear. Ventricular pulses were no longer transmitted to the left auricle. The left main bronchus was now more vertical than horizontal. The right ventricular outlet showed slight enlargement. The left ventricle was still markedly enlarged but appreciably smaller than previously. The patient's improvement progressed rapidly, and after two weeks of treatment he was again ambulatory and symptom-free. He was discharged on maintenance doses of digitalis with instructions to resume antiluetic therapy. When seen during a follow-up visit two months later he had regained his original weight and felt as well as he had prior to his illness.



FIG 5. A week after institution of treatment for failure. Marked reduction in size of left ventricle and left auricle. Retrocardiac space free.

Reconstruction of the story of the patient's illness led to the diagnosis of rheumatic heart disease, inactive, with enlarged heart and mitral insufficiency and stenosis, with the insufficiency preponderant. It appeared that congestive failure had complicated an initial acute respiratory infection. The occurrence of left-sided pneumonitis or pulmonary infarction early in the course could not be excluded. There



was no evidence of cardiovascular syphilis; the course and the electrocardiographic findings did not suggest myocardial infarction; and rheumatic activity was ruled out by the prompt and complete response to treatment of his failure.

### DISCUSSION

Dysphagia with enlarged left auricle has commonly been related to mitral stenosis in published reports. The enormously enlarged left auricle is regarded as a reflection of an unusual degree of valvular stenosis. Compression of the esophagus has been thought due to the counter-clockwise rotation of the cardiac axis that accompanies right ventricular hypertrophy and results in displacement of the enlarged left auricle posteriorly and to the right. Bloomfield postulated esophageal spasm as the mechanism in his patient's dysphagia, with compression by the auricle as the irritative factor and the vagus as the efferent pathway.

Nichols and Ostrum believed the cause of auricular dilatation to be replacement fibrosis of auricular muscle, with resulting loss of elasticity. The reversibility of the auricular enlargement, occasionally very prompt, is a point against this hypothesis. Another objection is that with widespread auricular fibrosis auricular fibrillation should be a uniform finding, yet two of the patients in whom the rhythm is recorded (Bloomfield's and ours) had regular sinus rhythm.

The fact that in our patient the signs of mitral stenosis were negligible and those of insufficiency marked led us to review the reported cases of dysphagia with left auricular enlargement. The following facts became evident: In all of these patients the left ventricle was massively enlarged, in all insufficiency or incompetency of the mitral valve was prominent, and all were in varying degrees of congestive failure. As in our patient, so in others, diminution in size of the left auricle and relief of dysphagia proceeded parallel with correction of failure and return of the dilated left ventricle to smaller size.

Such fluctuations in size of the left auricle, developing in a period of months and waning in weeks, cannot reasonably be attributed to the stable lesion of mitral stenosis years after the last endocardial insult. The significant change in these cases is marked dilatation of the failing left ventricle with increasing reflux into the left auricle through an incompetent mitral valve. The auricular dilatation would seem to be not merely a passive pouching-out of an inelastic fibrous sac but rather a useful compensatory mechanism in response to the increased intra-auricular pressure. The effect, in an auricle being filled from both ventricles, is that of achieving maximal contraction efficiency through lengthening of the muscle fibers (Starling's law). The systolic pulsation of the left auricle against the barium-filled esophagus seen in our patient was impressive visual evidence of the contribution made to intra-auricular pressure by regurgitation through a wide-open mitral valve. This systolic auricular pulsation could not be seen during later fluoroscopic examinations when the left ventricle had become smaller and the mitral valve ring presumably less widened.

The mitral stenosis found in all reported cases is, therefore, to be more accurately regarded as an incidental part of rheumatic valve scarring and not as the sole causative mechanism of extreme left auricular enlargement. Such extreme enlargement is due rather to the superimposed stress of a widely incompetent mitral valve developing with far advanced left ventricular dilatation.

The seven cases (eight with ours) of dysphagia caused by enlarged left auricle

reported in the literature in the past 20 years do not, of course, constitute more than a fraction of the number that have gone unrecognized. Vomiting in the course of congestive heart failure is generally attributed to congestion of the portal circulation. Often, too, the administration of digitalis adds another plausible reason for vomiting. The persistent, severe regurgitational vomiting of our patient associated with his dysphagia suggests the possibility that vomiting with esophageal compression may perhaps be more common than is generally realized. In cases where vomiting comes immediately after meals or occasionally interrupts the meal, fluoroscopic study of the barium-filled esophagus would seem justifiable to exclude compression by an enlarged left auricle.

### SUMMARY

Dysphagia is a rare complication of mitral valve disease; the case presented is the eighth with this condition reported in the past 20 years.

Review of previously described cases brings into prominence the marked enlargement of the left ventricle, the presence of mitral insufficiency and congestive failure in these patients, and the alleviation of dysphagia when management succeeds in reducing the size of the left ventricle. The essential mechanism in the production of a hugely enlarged left auricle appears to be not mitral stenosis *per se*, but marked insufficiency or incompetency of the mitral valve.

It is suggested that in addition to the two common explanations of vomiting during congestive failure, *i.e.*, congestion of the portal circulation and digitalis intoxication, a third mechanism may occasionally be involved, namely, compression of the esophagus by an excessively enlarged left auricle.

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### POLYARTERITIS NODOSA: A REPORT OF AN UNUSUAL CASE\*

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THE diagnosis of polyarteritis nodosa is being made with increasing frequency. The disease should be considered when a patient presents symptoms referable to several organs or systems, if such symptoms can be explained on the basis of multiple arterial occlusions. The following case of polyarteritis

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nodosa is presented because of the duration and variety of the symptoms, because the widespread manifestations suggested several separate diagnoses, and because of the difficulty in arriving at a final diagnosis.

### CASE REPORT

A veteran, 26 years old, was admitted to the hospital on August 7, 1946. He stated that two days previously, upon awakening from sleep in the morning, he bent over to pick up a shoe and was seized with a feeling of drunkenness. He noticed weakness of the right upper and lower extremities, together with numbness of the right side of the face, right arm and right leg. His speech was slurred.

The family history was non-contributory. The patient gave no history of venereal disease or allergy of any kind. In 1936 he had experienced swelling of the lower eyelids. This symptom recurred intermittently, and after a period of six months was followed by pain in the joints with swelling of the larger joints, muscle weakness, and fever as high as 101° F. A diagnosis was made of rheumatic fever, and the patient was kept in bed for a period of five months. Since that illness, there had been approximately semi-annual recurrence of joint pain and swelling with slight fever, during which times the patient had continued work. In addition, since the 1936 episode of arthritis, there had been the following: 1. Episodic appearances of multiple small, firm, red nodules in the subcutaneous tissues of the arms, legs, hands and feet. The nodules usually disappeared after one week. 2. Frequent minute, red spots which disappeared on pressure, on the skin of the chest. 3. Intermittent bilateral posterior flank pain. 4. Episodes of transient pain and weakness of muscle groups in the different extremities. The pain was described as dull and was relieved by aspirin.

The patient entered Military Service in January 1941, and served as a jeep driver and artillery soldier. In September 1941, he suffered an attack of "influenza" accompanied by mild joint pain, and was in a hospital for six weeks. Two days after his release from the hospital he was readmitted because of pneumonia. During this time he had pains in the joints of the hands and feet and recurring subcutaneous soft swellings over dorsums of hands and feet. Following recovery from pneumonia, there was recurrence of swelling of the eyelids, intermittent fever as high as 101° F., and bilateral posterior flank pain. Polyuria and gross hematuria were not present, but because of the presence of albumin, casts, and red cells in the urine, edema of the face, impaired renal function, and rapid sedimentation rate, a diagnosis of chronic parenchymatous nephritis was made. The patient was also thought to have rheumatic fever. He was separated from the service by Certificate of Disability Discharge in August 1942.

Subsequently, the patient had been unable to work steadily because of symptoms. Intermittent joint pains, with swelling of the knees and ankles, continued until present admission. He had worked at intervals as an aircraft inspector, typewriter repairman and welder. In April, 1946, after two hours of exposure to light from a welding torch, he suddenly became completely blind for a period of 30 minutes. The company doctor told him that the blindness was due to the welding light rays. Beginning 10 days later, the patient had double vision which lasted for two or three months. Since the attack of blindness, he had had dull frontal, temporal and occipital headache every morning on awakening, lasting one to several hours.

In addition, during the two years prior to the present hospitalization, the patient had had episodes of vomiting one to four times a month and usually occurring one hour before meals. During the two weeks preceding hospitalization, he had had nausea two hours after meals once or twice daily. Appetite was fair. There had been no hematemesis. Severe abdominal pain had occurred only once and at that

time, in 1944, an appendectomy was performed. Patient complained of being constantly underweight and lacking in energy. In the six months before admission there had been a daily cough productive of white sputum.

*Physical Examination:* Patient was small in stature, fairly developed, but undernourished. Oral temperature was 98.4° F. Musculature was flabby. Patient appeared 10 to 20 years older than stated age. There were small, non-discrete, cystic-feeling subcutaneous swellings about one-half inch in diameter over the knuckles of each hand. Dilated venules were present in the skin of face and a few spider angiomas were present over the posterior portion of the neck. There was a slight yellowish tinge to the skin. The pupils reacted to light and accommodation. Nystagmus was present in the superior vertical, and horizontal planes. The ocular fundi were normal. Examination of the heart and lungs yielded no abnormal clinical findings. Pulsations of the peripheral arteries were present and normal. Radial pulse rate was 76/min. Blood pressure readings were as follows: right arm—100/70; left arm—96/70. The abdomen was essentially normal. Small posterior cervical lymph nodes, submental nodes, large soft axillary nodes and a few small soft inguinal nodes were found. There was tenderness but no heat or redness about the joints of the right hand, the right elbow joint, and both shoulder joints. No muscular atrophy was noted, but muscular weakness was found in the right upper and lower extremities.

Neurological examination revealed no pupillary irregularities. There was slight flattening of the musculature of the left side of face but no definite evidence of seventh nerve involvement. The tongue deviated to the right side, and slight slurring of speech was present. There was decrease of muscle power of minimal to moderate degree on the right side of the body including large as well as small muscle groups. Sensory findings included hypesthesia of the right side of the face and entire right side of the body. Deep reflexes were hyperactive on the right side (ankle, knee, biceps, triceps, and periosteal reflexes). Right ankle clonus and right Babinski reflexes were present. Questionable right Tremnor reflex was present. The right superior and inferior abdominal reflexes were absent. The Romberg sign was not present.

*Laboratory Findings:* On admission, blood count was as follows: white blood cells 6,150; hemoglobin 10.0 gm. per cent; red blood cells 4,130,000; neutrophils 66 per cent; lymphocytes 24 per cent; monocytes 4 per cent; eosinophiles 6 per cent.

Eight blood counts revealed the white blood cells to vary from 7,300 to 12,600 per cu. mm. The eosinophile count was within normal limits except in one instance when eosinophiles numbered 8 per cent. Hemoglobin determinations varied from 10 to 11.5 grams, and red blood cells approximated 4,100,000 per cubic mm. of blood. Twenty-two urinalyses showed the following: Specific gravity varied from 1.000 to 1.010. Albumin was graded from one to three plus, and in a few specimens was found to be absent. Microscopic examinations of urinary sediment were usually negative, but under high power a few white blood cells, less than five red blood cells, and a few granular casts per field were occasionally seen.

Urine concentration test showed the greatest specific gravity to be 1.011. Urea clearance was 95 per cent of normal. Non-protein nitrogen was 37.5 mg. per cent, blood urea nitrogen, 16.3 mg. per cent. Kahn test for syphilis was negative. Spinal fluid was normal. Seven sedimentation rates varied from 25 to 32 mm./hr.

Routine agglutination tests (undulant fever, tularemia; Weil-Felix, *E. typhosa*, *S. paratyphi*, *S. schottmuelleri*) were negative. Sputum smears for acid fast bacilli: negative. Total serum proteins, albumin-globulin ratio and van den Bergh test were within normal limits. Blood cell sickling test was negative. Electrocardiograms were normal.

Roentgen-ray examination of the skull, right knee, ankle, hand, shoulder and chest revealed no abnormalities. Intravenous pyelogram showed incomplete visualization of the right upper urinary tract but no abnormality in size or position of either kidney

was seen. Roentgen-ray examination of the upper gastrointestinal tract revealed no abnormality.

*Course in Hospital:* On August 9, two days following admission, the patient's right hemiparesis and slurred speech were lessened, but the nystagmus, tongue deviation, right sided weakness, hypesthesia and hyperreflexia continued unchanged. In late August, the patient was walking without apparent difficulty, and slurring of speech was minimal. Right muscle weakness, hyperreflexia and hypesthesia were still present. By the first of September slurring of speech had disappeared, right sided muscle weakness was lessened, but the other signs still were present. In mid-September, nystagmus was still present, stronger with vision to the right, and the right abdominal reflexes had reappeared weakly. In early October, the superior and bilateral excursion of nystagmus had become diminished; there was no sign of hypesthesia or muscle weakness, and the previously noted right ankle clonus and Oppenheim reflex were now absent. The right Babinski reflex was variable. Periosteal and biceps reflexes of the right upper extremity and the right knee jerk were slightly exaggerated.

Throughout the hospital stay there were transient episodes of pain and weakness in the upper extremities; the last such episode was early in October, when pain and weakness of the left arm and left hand occurred over a two-day period. This was not associated with hypesthesia or other neurological signs in the affected extremities.

Throughout the hospital stay oral temperatures were normal except for one spike to 100° F. Radial pulse rates varied from 60/min. to 116/min., with usual range from 70/min. to 90/min.

Upon admission and again four weeks later, there were noted patchy, soft, ill-defined, slightly raised, cystic-feeling, slightly tender subcutaneous swellings over the metacarpophalangeal joints of both hands. The overlying skin was slightly more red than the color of the surrounding skin, but not perceptibly warmer. On each occasion, the lesions disappeared within one week. In mid-September two small, discrete, firm, tender nodules, evidently different from the swellings described above, appeared in the subcutaneous tissue of the volar surface of the right forearm and disappeared within two days, followed after several days by the appearance of two more nodules on the medial aspect of the right forearm. The latter were excised. Nodules continued to appear and disappear over both forearms, and occasionally some appeared on the chest anteriorly, resolving within 24 hours. At the end of September a few pin-point, red spots were noted on the skin of the anterior chest. These did not blanch on pressure and did not look exactly like petechiae. The patient stated that such spots had occurred transiently during the past 10 years.

*Microscopic Description of Resected Nodule:* The greater portion of the tissue consisted of adipose tissue with no distinguishing characteristics. In one area, there was a small artery, the lumen of which was occluded by a thrombus. One segment of the arteriolar wall had been destroyed by an acute inflammatory process which involved the entire wall of the artery and the periarterial tissue. The predominating cell was the neutrophile, but numerous eosinophiles were present.

*Diagnosis:* Acute arteritis consistent with polyarteritis nodosa. The lesion is reproduced in figure 1.

No specific treatment was instituted. The patient was released to his own care in October 1946. He returned to the hospital in March 1947 because of progressive weakness. At this time, physical examination was virtually the same as recorded previously, with the exception that there was an apparent decrease in general muscle strength. The patient stated that nodules had occurred in the subcutaneous tissues irregularly. Shortly after the second admission to the hospital several such lesions appeared and one was excised from the medial surface of the left thigh in its middle third. The histologic appearance of this lesion was similar to that of the previously examined one.

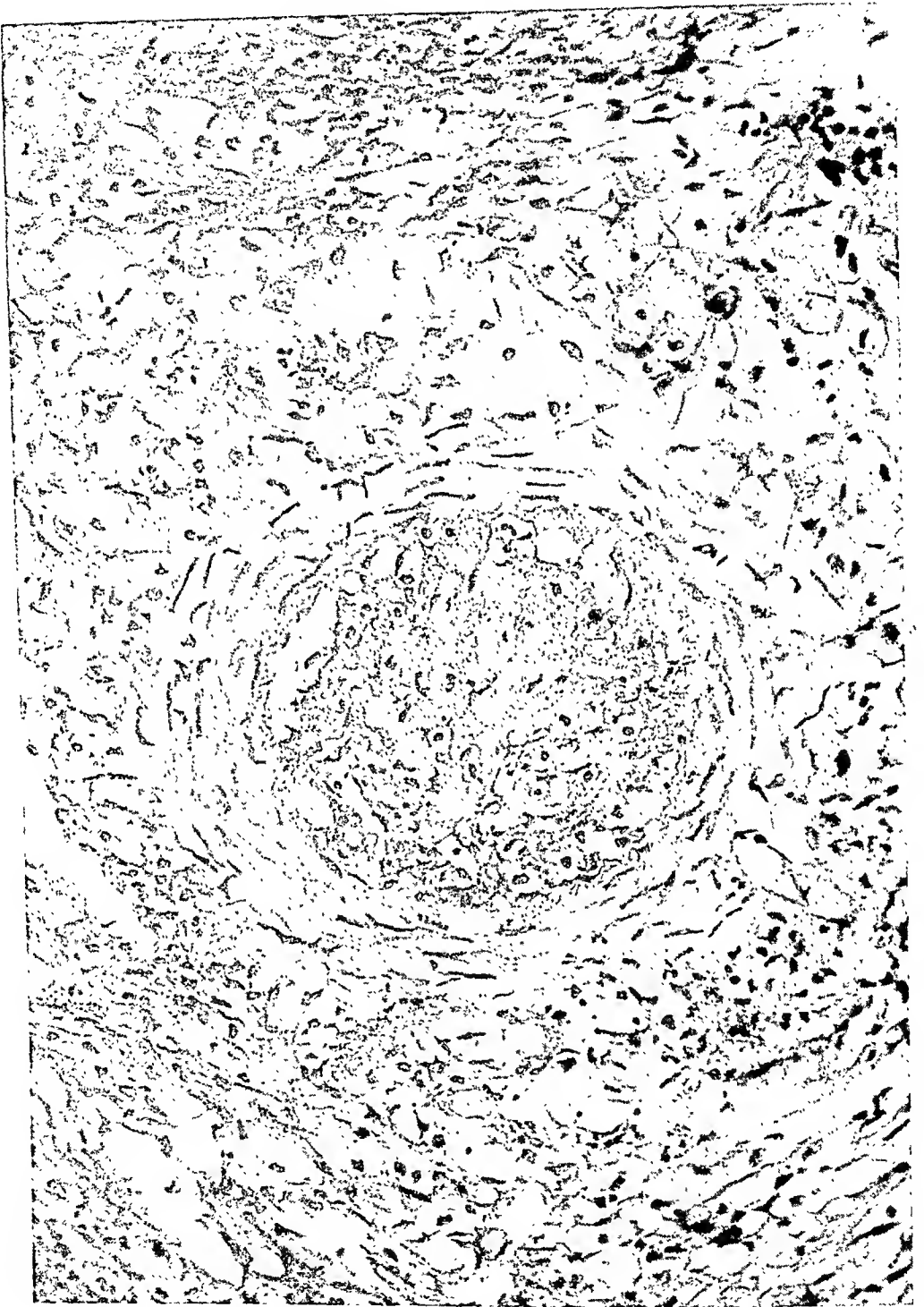


FIG. 1.

#### COMMENT

The diagnosis of polyarteritis nodosa seems justified in this case because of the clinical manifestations and the histologic features of the nodules excised from the subcutaneous tissues of the right forearm and left thigh. While doubt exists as

to the date of onset of polyarteritis nodosa in this case, it is very probable that the earliest manifestations precipitated the illness diagnosed as rheumatic fever 10 years before the present hospitalization. It is logical to assume that this disease was responsible for the symptom complex for which the patient had been observed in 1942.

Several excellent reviews of the subject of polyarteritis nodosa have been published recently.<sup>1-6, 12</sup> We wish to emphasize the difficulty which the physician may have in arriving at a positive diagnosis in any given case. In the present case, diagnoses of rheumatic fever and chronic glomerulonephritis had been made previously, and our initial impression had been that the patient was suffering from chronic glomerulonephritis and multiple sclerosis. The latter diagnosis was prompted by the history of transient amaurosis and the fact that the neurologic manifestations indicated multiple lesions in the central nervous system. Closer examination, however, revealed that the entire clinical picture could be best explained by one diagnosis: polyarteritis nodosa. The appearance of subcutaneous nodules afforded an opportunity to verify the diagnosis.

The occurrence of transient amaurosis may well have been associated with a lesion of polyarteritis nodosa. Transient blindness has been rarely reported in polyarteritis nodosa.<sup>2, 12</sup> We feel the blindness was unrelated to the occupation of welding inasmuch as ordinarily the so-called arc flash injury to the eyes is not manifested by transient amaurosis, but rather by a conjunctivitis lasting 24 to 48 hours. In addition it will be recalled that within a period of 10 days after transient blindness had occurred abnormalities of the extra-ocular muscles had occurred. Amblyopia, nystagmus, hemiparesis; and numerous other central nervous system signs such as cerebellar signs, convulsions, signs of meningeal irritation, decerebrate rigidity, conjugate deviation of the eyes, anisocoria, facial nerve palsy, and subarachnoid hemorrhage have been reported in polyarteritis nodosa.<sup>2, 4, 5, 12</sup>

In favor of the diagnosis of polyarteritis nodosa in this case, and against the diagnosis of multiple sclerosis were:

1. The fact that the patient felt ill and definitely was concerned about his condition. Individuals with multiple sclerosis, on the basis of the experience of one of us (K. E.), in the great majority of cases do not feel ill and tend to minimize the incapacities arising from their condition.
2. The fact that although right hemiparesis decreased considerably over a two month period, it did not stop abruptly. If neurological signs in multiple sclerosis remit, they tend to remit abruptly rather than gradually decrease in intensity (per K. E.).
3. The multiplicity of symptoms and system involvement, the likelihood being that the multiple involvement was due to one disease rather than to many diseases.
4. Transient eosinophilia.
5. Elevation of sedimentation rate.
6. The fact that episodes of transient numbness occurring in the extremities over the last 10 year period were accompanied by pain in the affected extremity, and were evidently due to involvement of peripheral nerves rather than to involvement of the central nervous system.
7. Final confirmation of diagnosis of polyarteritis nodosa by a biopsy of subcutaneous nodules.

This case is of particular interest because of the occurrence of symptoms leading to a diagnosis of rheumatic fever on at least two different occasions. The coincidence of the symptom complexes of rheumatic fever and polyarteritis nodosa is not infrequent and deserves more attention, especially since Rich and his associates<sup>7, 8</sup> have noted lesions similar to those of rheumatic fever and polyarteritis nodosa in the course of the production of hypersensitivity reactions in animals. Furthermore, a relationship each to the others of rheumatic fever, renal diseases, and polyarteritis nodosa has been suggested by the experimental work of Selye.<sup>9</sup> In well-controlled experiments Selye was able to produce simultaneously in the same rats lesions of rheumatic carditis ("Aschoff's nodules"), malignant nephrosclerosis, and visceral polyarteritis by the use of large doses of desoxycorticosterone acetate or alkaline pituitary extract in unilaterally nephrectomized rats receiving 1 per cent sodium chloride solution to drink ad lib.<sup>10, 11</sup> An important factor in the production of the various lesions may have been sodium chloride retention.

### SUMMARY

A case of polyarteritis nodosa of 10 years' duration is presented. The disease was initiated by an illness simulating rheumatic fever. Subsequently, a diagnosis was made of chronic glomerulonephritis. Finally a transient amaurosis, hemiplegia, and nystagmus occurred and the patient was admitted to a hospital where a diagnosis was made of polyarteritis nodosa. This was confirmed by histologic study of nodules excised from the subcutaneous tissues.

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## HYPERPARATHYROIDISM—SIMULATING PAGET'S DISEASE \*

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THE consensus among investigators interested in bone disease is that generalized osteitis fibrosa cystica (Von Recklinghausen's disease) and osteitis deformans (Paget's disease), represent two definite, independent, clinical entities.<sup>1, 2, 3, 4</sup> The former, due to hyperparathyroidism, has a clinical, roentgenologic, and biochemical picture which is distinct from the latter, whose cause is unknown and which manifests its own clinical and laboratory characteristics. This view applies to practically all of the cases presenting the respective picture of these two disorders. There are, however, several reports of cases in the literature which do not quite fit into either category but which appear to be examples of cases which exhibit coexistent features of hyperparathyroidism and Paget's disease. Albright, Aub, and Bauer first described these cases in America in 1934. In addition to reporting two of their own cases, they quote two reports from the continental literature of undoubted hyperparathyroidism which presented such marked thickening of the skull that the additional diagnosis of Paget's disease was entertained. By presenting pathological findings of Von Recklinghausen's disease in a 61 year old woman with an alleged sarcoma, Berblinger<sup>6</sup> made the first observation that healing in hyperparathyroidism may lead to hyperostosis of the skull and other bones.

The purpose of this paper is to describe another case in which the rare combination of bone destruction and hyperostosis were present.

### CASE REPORT

R. J., a 39 year old married colored woman, was admitted to Goldwater Memorial Hospital in January, 1944, because of progressive cardiac failure and invalidism resulting from an old left hemiplegia. Her illness began in 1940 when she sought admission to City Hospital because of complaints referable to her respiratory tract, and pain and limitation of motion in her right knee. Examination at this time revealed a poorly nourished, chronically ill patient with a blood pressure of 198 mm. Hg systolic and 120 mm. diastolic. According to the hospital transcript, other positive findings included a nasopharyngitis and an enlarged heart. Roentgen examination of the chest and of the right knee at this time revealed (Dr. Kraft): "Numerous osteofibrotic changes in the ribs especially in the region of the costochondral junction. Similar changes were noted in the upper end of the right tibia." In view of these findings, the patient was investigated from the standpoint of a generalized bone disease. Subsequent roentgenograms of the skeleton revealed "osteofibrotic changes in the pelvic bones, long bones of the extremities and phalanges of the hands. The calvarium of the skull was markedly thickened giving a cotton-wool appearance as seen in Paget's disease" (figures 1, 2, 3). Blood counts and urinalyses revealed no abnormalities. Hypercalcemia, hyperphosphatemia and increased serum phosphatase activity were found on two examinations (table 1). A rib biopsy yielded the histologic

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picture of healing osteitis fibrosa. An exploratory operation was performed and a markedly enlarged parathyroid gland was discovered, and removed. Histologic section showed an encapsulated adenoma with numerous groups of water clear cells scattered throughout the parenchyma, and many cystic areas filled with a colloid-like substance, with the pathological diagnosis of adenoma of the parathyroid gland.

The postoperative course was uneventful, and one week following surgery, the calcium and phosphorus levels of the blood were found to be normal, whereas there still remained an increase in the serum phosphatase. Chemical studies of the blood were again made one month after operation, and the levels were found to be unchanged.

The patient was discharged on May 19, 1940 to the City Hospital Clinic. She remained well for about one year, but then, because of signs of increasing heart failure, she applied for admission to another municipal hospital, where a diagnosis of essential hypertension and hypertensive cardiovascular disease was made. On appropriate therapy her status improved to such extent that she was able to leave the hospital about a month later. She remained fairly well after this for a period of three years. In 1943 she again sought hospitalization because of the return of the symptoms of cardiac failure. Again there was good response to specific treatment and she left the hospital about three weeks later.

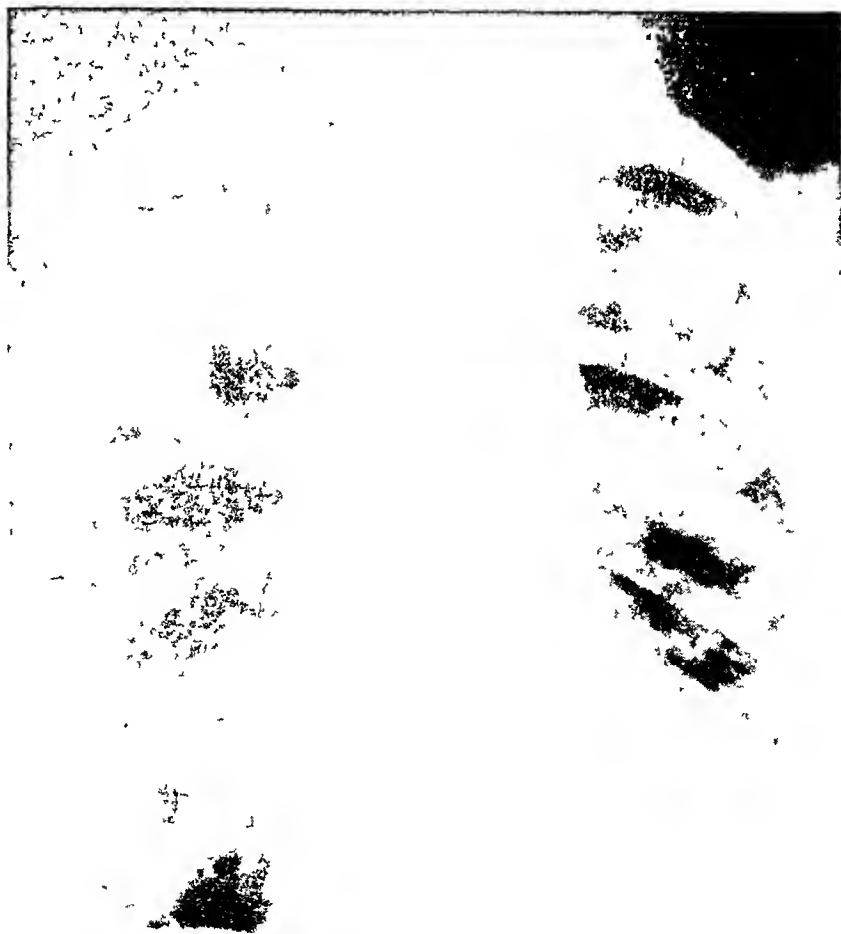


FIG. 1. Roentgenogram of chest showing numerous osteofibrotic changes in the ribs, especially in the region of the costochondral junction.

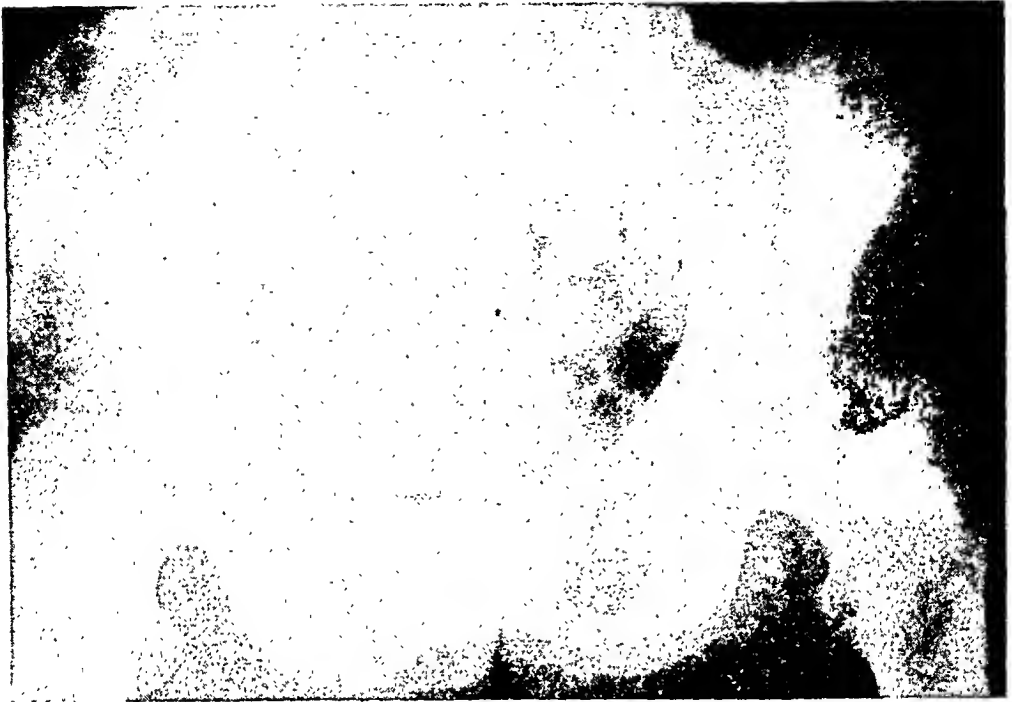


FIG. 2. Roentgenogram of pelvis showing osteofibrotic changes and thickening enlargements of the involved bones.

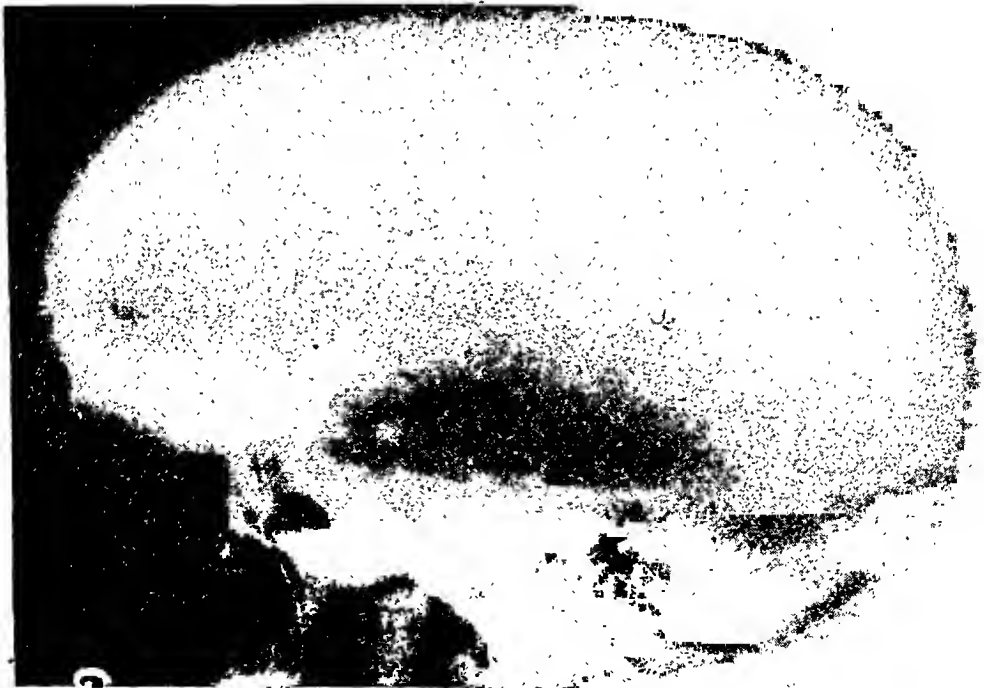


FIG. 3. Roentgenogram of the skull demonstrating marked thickening of the calvarium with a "cotton-wool" appearance.

TABLE I  
Blood Chemistry Studies

Serum				
Date	Calcium (mg. %)	Phosphorus (mg. %)	Alk. Phosphatase (Bodansky units)	Blood Urea N (mg. %)
3/ 1/40	16.2	1.8	14.0	16
3/ 5/40	16.6	2.3	12.1	.
4/18/40	Operation—Parathyroid tumor removed.			
4/25/40	10.4	3.1	19.3	
5/13/40	8.4	4.1	14.0	
1/20/45	10.1	4.2	11.2	36
1/30/45	9.7	2.6	8.4	
4/19/45	10.5	3.8	8.0	17
11/13/45	10.5	2.9	5.3	19

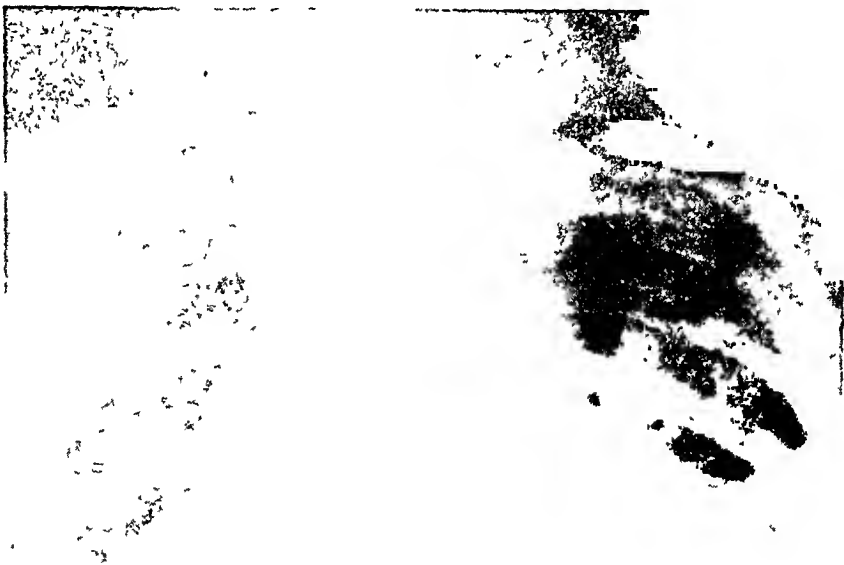


FIG. 4. Roentgenogram of the chest shows marked cardiac enlargement. The thoracic cage shows Pagetic bone change with retraction of the axillary portion of the right base.



FIG. 5. Roentgenogram of the skull reveals marked thickening of the vault with no destructive changes. The base of the anterior middle fossa also shows sclerotic bone changes.

On January 2, 1944, the patient suddenly became unconscious, and was admitted to Goldwater Memorial Hospital because of a left hemiplegia. Physical examination at this time revealed a 39 year old colored woman lying propped up in bed in no acute distress. There was bilateral exophthalmos and left facial weakness. The head was enlarged with frontoparietal bossing. Fundusoscopic examination showed moderate hypertensive arteriosclerotic changes with normal discs. The right chest was larger than the left in the anteroposterior diameter and moderate kyphoscoliosis was present. There were many fine moist basilar râles in both lungs. The heart was markedly enlarged, the point of maximum impulse being in the sixth interspace in the anterior axillary line. There was a loud blowing systolic murmur heard best at the apex and transmitted all over the precordium. The blood pressure was 140 mm. Hg systolic and 102 mm. diastolic in both arms. Abdominal examination revealed a tender, smooth edged, firm liver six centimeters below the right costal margin. A left-sided hemiplegia was present. The remainder of the physical examination was essentially negative. Laboratory findings revealed a normal hemogram and urinalyses except for a fixed specific gravity at 1.017, as determined by concentration tests. Blood sugar, cholesterol and total proteins were within normal limits as were the blood calcium and phosphorus on repeated examinations (table 1). The serum alkaline phosphatase was at the upper limit of normal. The venous pressure was elevated and the circulation time was delayed from arm to lung and arm to tongue. Electrocardiograms demonstrated left axis deviation with changes indicative of myocardial damage. Interpretation of the roentgenograms made five years after her parathyroidectomy was (Dr. H. K. Taylor): "Examination of the chest shows marked enlargement of

the heart to the right and to the left with the configuration such as to suggest enlargement of all the chambers. The thoracic cage shows Pagetic bone changes with retraction of the axillary portion of the right base. The bones of the pelvic girdle show an increase in density due to Pagetic bone changes. The skull shows marked thickening of the vault with no destructive changes. The base of the anterior middle fossa also shows sclerotic bone changes. In the middle shaft of the femur, there is an area of increased bone density. There is an old healed fracture of the shaft of the left radius. Examination of the abdomen reveals no abnormality of the kidneys" (figures 4, 5, 6).



FIG. 6. Roentgenogram shows an increase in density of the bones of the pelvic girdle due to Pagetic changes.

## DISCUSSION

Five years prior to present admission the patient presented the clinical, roentgenologic, and biochemical picture of hyperparathyroidism except for the roentgenographic appearance of the skull which was compatible with that of Paget's disease. On surgical exploration, an adenoma of the parathyroid gland was found and the diagnosis was corroborated by histologic section. The blood chemical findings reverted to their normal status in the immediate postoperative period except for the serum alkaline phosphatase which required a long interval of time before returning to normal.

Five years after parathyroidectomy, the patient presents roentgenologic evidence of Pagetic changes in the skull, pelvis, femora, ribs and fingers. In addition, the blood calcium, phosphorus, and alkaline phosphatase are normal. In classifying this case, it was necessary to determine whether this was a patient with hyperparathyroidism associated with Paget's disease or one of the unusual cases of hyperparathyroidism whose recalcification and healing manifests itself in a form which is roentgenologically indistinguishable from Paget's disease. It is felt that because of the relatively young age of the patient, the reversion to normal of the serum alkaline phosphatase, the unusual distribution of the lesions especially in the ribs and fingers, and the proved diagnosis of hyperparathyroidism, this is a case of von Recklinghausen's disease which on healing acquired the bone picture of Paget's disease.

The author wishes to thank Dr. I. Snapper of Mount Sinai Hospital, New York, New York, for his suggestions and helpful advice.

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## COLD AUTOHEMOLYSIS ASSOCIATED WITH RAYNAUD'S SYNDROME: REPORT OF CASE \*

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COLD autohemolysis denotes the presence in the blood of an immunologic reactor (autohemolysin), which at low temperatures unites with red cells to produce a hemolytic reaction. Hemoglobinemia and, if hemolysis is sufficiently marked, hemoglobinuria will result.

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Paroxysmal hemoglobinuria has been frequently recognized since its first description by Dressler<sup>1</sup> in 1854. It is known to occur following several conditions: exposure to cold, physical exercise (March hemoglobinuria), ingestion of the fava bean, and in chronic hemolytic anemia (syndrome of Marchia Fava-Michaeli). Gull<sup>1</sup> in 1866 first noted the relation of the exposure to cold to this syndrome, and in 1880 Rosenbach<sup>1</sup> demonstrated an attack in a patient by immersion of the feet in ice water. Kussner,<sup>1</sup> in 1879, by observing the color of the serum during an attack established the fact that hemoglobinemia and intravascular hemolysis occur. Lesser contributions were made by others before the end of the century, but the basic mechanism of cold autohemolysis was not elucidated until 1904 when Donath and Landsteiner<sup>1</sup> demonstrated by a simple *in vitro* test that the blood of these patients contains an autohemolysin. They proved that a mixture of the patient's serum and cells immersed in ice water for 30 minutes was not altered by the chilling alone, but that after warming the specimen free hemoglobin occurred in the supernatant serum. This constitutes the Donath-Landsteiner test. It is based on the discovery by these immunologists that at low temperatures a lysin unites with the red cells and that on warming in the presence of complement lysis of the cells occurs. This is the fundamental explanation of the *in vivo* mechanism of paroxysmal hemoglobinuria due to exposure to cold.

The essential cause of this phenomenon is accepted to be syphilis. Either serological or clinical evidence of syphilis has been present in practically all reported cases of the disease. A review of the literature between 1905 and 1925 by Donath and Landsteiner<sup>2</sup> revealed that, of 97 cases of unqualified paroxysmal hemoglobinuria reported, 95 showed evidence of either clinical or latent syphilis. However, numerous investigators have proved that only a small percentage of patients with syphilis have hemoglobinuria. Dill, Douvros and Isenhaur<sup>3</sup> found only one positive Donath-Landsteiner test among 360 syphilitics representing all stages of the disease. Congenital syphilitics appear to be more liable to develop this disease than do individuals with acquired syphilis.

The association of vasomotor phenomena with paroxysms of cold hemoglobinuria has been observed. Hives and urticarial wheals often occur, and Raynaud's syndrome is frequently associated. Mackenzie<sup>4</sup> reports that two of the five patients observed by him had vasomotor symptoms. The patient to be presented showed marked vasomotor disturbances with local gangrene of the finger tips.

#### CASE REPORT

The patient, a 25 year old Negro soldier, was first admitted to the Station Hospital on May 26, 1944, complaining of low back pain and the passage of dark red urine. Examination on the following day failed to reveal discoloration of the urine, and study of the urinary and musculoskeletal systems failed to reveal any abnormalities, so that he was returned to duty on June 27, 1944.

He was readmitted on August 26, 1944 because of pain in the fingers.

History obtained on the second admission revealed that while at his home in Indiana in 1937 and again in 1938 he had voided dark red urine, each attack occurring during cool weather of autumn and for only one voiding. He did not recall the presence at that time of systemic symptoms or backache. Since 1939 his fingers had become very painful while going to and from his work during cold weather, the pain persisting for several hours after warming the extremities. As long as he could re-



member he recalled having recurrent pain in the lower back of no known association with exposure to cold.

In January 1944, while walking guard duty at an Army station in Indiana, he suffered extreme pain in the fingers, toes and ears. At that time the atmospheric temperature was between 20° F. and 30° F., and because of the pain he was relieved of duty after two and one-half hours. Within six hours the persistence of severe pain and occurrence of swelling of the fingers, toes and ears led him to report on sick call where tablets for pain were given him. He remained in his quarters and the symptoms disappeared by the following day. He did not recall having noticed the passage of red urine or having had systemic symptoms. For the remainder of the winter of 1944 he was assigned to indoor duty because of his sensitivity to cold. In April 1944 the patient was transferred to a station in Georgia, where he performed outdoor duty. The weather was variable, and on the cooler days he experienced mild aching of the fingers. After one hour of drill on May 25, which was a moderately warm day, he passed urine of dark red color and experienced considerable back pain, which reason prompted his first admission to the Station Hospital (referred to above).

On July 28, 1944 while on a furlough aboard an air-conditioned train passing through Ohio, an episode of vomiting, headache, generalized pain in the abdomen and back, and pain and swelling of the fingers occurred. Soon after the onset of these symptoms the patient experienced chilliness and sweating, but failed to notice discoloration of the urine. On the following day he felt normal except for pain in the fingers which persisted. On August 1 the nails of the left hand became yellow and during the next few days changed to a reddish brown color. He reported to a nearby Army station dispensary where he was given medication to relieve the pain. He returned from furlough and was readmitted to the Station Hospital on August 26.

Prior to induction in February 1944 the patient made paper die casts in his home city of Indianapolis, Indiana. He denied using alcohol, but smoked 30 cigarettes daily. Family history revealed that a sister, with whom he had close contact, died of "lung trouble" in 1940.

Medical history prior to the present illness revealed that since childhood he had experienced recurrent attacks of hives. In 1939 a chancre occurred, not followed by a rash. No antisyphilitic therapy was received until February 1944, and since that time he had received regularly biweekly bismuth and mapharsen in alternating courses.

Physical examination on August 26, 1944 showed no abnormalities other than of the fingers. The nails of the left hand were atrophic, concave and very thin and the matrix was of a dark mahogany color. The fingertips were so tender that he was unable to use them. The hands were moist and warm, and there was no gross alteration in skin temperature. The radial and pedal pulses were normal. Blood pressure was 122 mm. of Hg systolic and 80 mm. diastolic. Cold-pressor test, as described by Hines,<sup>5</sup> produced a normal blood pressure response. The electrocardiogram was normal. Urologic and orthopedic studies were unrevealing.

Beginning on September 6, openings appeared beneath the tips of the involved nails and purulent fluid exuded, leaving the distal portion of the nails separated from the matrix (figure 1), over which new nails later developed. On October 1 the patient experienced pain in the lower back and in all of the fingers, especially severe in the tips of those of the right hand, requiring analgesic medication. On the following day the right hand was observed to be cold, wet, and very sensitive to touch; and after 48 hours the nails had taken on a mahogany color (figure 2), following which they slowly went through the progressive color and atrophic changes which had previously occurred on the left. No elevation of temperature or leukocytosis was detected, and the urine gave a negative guaiac test on October 2. A similar, less severe attack again involved the right hand after the cool morning of October 10.



FIG. 1. Photograph of fingertips, left hand, showing late stage of ischemic necrosis (Photo by U. S. Army Signal Corps).

On October 12 the patient was exposed to  $4.5^{\circ}\text{C}$ . in a refrigerator for 30 minutes, during which he complained bitterly of pain of the ears, fingers, and toes, which afterward only gradually subsided. No systemic symptoms, leukocytosis or hemoglobinuria were found following the exposure. During the ensuing week, pain and numbness of the fingers were more marked than before and a newly formed nail of the left hand became discolored.

Desensitization to cold was attempted between October 28 and November 20 by means of immersion of all extremities for 20 minutes daily in water of gradually reduced temperatures, beginning at  $82^{\circ}\text{F}$ . and ending at  $42^{\circ}\text{F}$ . Penicillin, 2,400,000 units in intramuscular doses of 40,000 units each at three hourly intervals, was ad-



FIG. 2. Photograph of fingertips, right hand, showing early stage of ischemic necrosis (Photo by U. S. Army Signal Corps).

ministered, beginning on November 28. During the latter treatment the patient experienced a chill, with a temperature of 101° F., and pain in the fingers and back lasting for six hours. Unfortunately, no laboratory studies were made at that time. On November 11 and 28, while the lowest weather temperatures ranged between 36° F. and 44° F. (patient was often in the unheated corridors) he suffered attacks of pain in each foot which subsided after three to four days without abnormal findings. On December 26, while on furlough in Indianapolis, he walked less than one block distance when the temperature was about 38° F., and immediately experienced aching and numbness of the fingers with yellowish discoloration of the nails of the right hand on the following day. On his return to the hospital on December 29, these nails were observed to be orange-red, and on January 11 to be mahogany red.

On January 16, 1945 the patient was discharged from the service and sent to a Veterans Administration Hospital near his home, from which he soon signed his release. Further efforts to locate him have been unsuccessful.

*Laboratory Data and Special Studies.* Repeated examinations of the centrifuged urine revealed: specific gravity of normal range, albumin and sugar negative and microscopically normal except for 17 to 20 white blood cells per high-power field on August 26. Benzidine and guaiac tests were negative when performed on the urine following attacks of digital pain.

A blood count on August 29, during the period of most marked involvement of the fingers, was as follows: 5,200,000 erythrocytes per cu. mm.; hemoglobin 95 per cent (Sahli); 11,900 leukocytes per cu. mm. with 53 per cent neutrophils, 42 per cent lymphocytes and 5 per cent eosinophils. Repeated blood counts following other attacks of digital pain gave normal results. Erythrocyte sedimentation rate determinations (Wintrobe) varied between 2 mm. and 10 mm. in one hour. Red cell fragility determination at 4° C. revealed hemolysis to begin at 0.44 per cent and to be completed at 0.36 per cent solution of sodium chloride. The blood was Rh negative.

Serodiagnostic tests for syphilis performed at the laboratories of the Station Hospital and of the Army Medical Center, Washington, D. C., were positive. Repeated batteries of tests performed at the latter laboratory (including the Kline, Kahn, Kolmer, Boerner-Jones-Lukens and Mazzini tests) were uniformly positive. Blood taken following penicillin therapy continued to show positive results of un-reduced titer when subjected to the quantitative Kahn and Kolmer tests. Spinal fluid examination on October 11 revealed the following: one cell (lymphocyte) per cu. mm., absent globulin, total protein 28.2 mg. per cent, and negative Kahn reaction.

TABLE I  
Tube Set-Up for the Donath-Landsteiner Test

Tube	Pt.'s Serum	Pt.'s RBC	Control Serum	Control RBC	Complement	Saline
1	0.5 c.c.	0.2 c.c.			0.2 c.c.	0.1 c.c.
2			0.5 c.c.	0.2 c.c.	0.2 c.c.	0.1 c.c.
3	0.5 c.c.			0.2 c.c.	0.2 c.c.	0.1 c.c.
4		0.2 c.c.	0.5 c.c.		0.2 c.c.	0.1 c.c.
5		0.2 c.c.			0.2 c.c.	0.6 c.c.
6				0.2 c.c.	0.2 c.c.	0.6 c.c.

Patient's Serum = patient's fresh serum.

Patient's RBC = 5% suspension of washed red blood cells of patient.

Control Serum = fresh serum from a normal individual of same blood group as patient.

Control RBC = 5% suspension of washed red blood cells from individual of same blood group as patient.

Complement = a 1:10 dilution of fresh guinea pig serum.

Saline = physiological saline.

The Donath-Landsteiner test was performed in accordance with the modified procedure described by Wintrobe.<sup>6</sup> The tubes were set up as shown in table 1. All tubes were immersed in ice water for 30 minutes, at the end of which no changes were noted. The tubes were then immersed in a water bath at 37° C. for 30 minutes with the following results: Hemolysis in tubes 1 and 3; no hemolysis in tubes 2, 4, 5 and 6. Tube No. 1 was set up using the patient's spinal fluid instead of serum; and following the same procedure no hemolysis was observed.

Titration of the above procedure were set up as follows: Serial dilutions of the patient's serum were made ranging from 1:2 to 1:128, each serum dilution of which was placed in a tube containing the patient's red cells, complement and saline in the same quantities used in tube No. 1 of table 1. Six sets of varying dilutions were prepared, each set being placed at different temperatures for 30 minutes and then at 37° C. for 30 minutes. All tubes were then read for hemolysis. Results are shown in table 2. Another titration was performed for hemolysin using the same technic as previously with the exception that the chilling period was reduced to six minutes. No hemolysis was observed in any of the tubes. A comparison of the hemolysin titers as determined in vitro for different dates is presented in table 3.

TABLE II  
Serial Dilution Titration of Donath-Landsteiner Test at Different Temperatures

Temp.	1:2	1:4	1:8	1:16	1:32	1:64	1:128
0° C.	+++	++	+	±	±	—	—
4° C.	++	++	+	±	±	—	—
8° C.	++	+	±	—	—	—	—
14° C.	—	—	—	—	—	—	—
29° C.	—	—	—	—	—	—	—
37° C.	—	—	—	—	—	—	—

TABLE III  
Comparison of Hemolysin Titers on Different Dates, Using 1.0 c.c. Water at 0° C. for Fixation

Date	1:2	1:4	1:8	1:16	1:32	1:64	1:128
Oct. 5	+++	++	+	±	±	—	—
Oct. 20	++++	+++	++	±	—	—	—
Nov. 25	+	—	—	—	—	—	—
Dec. 1	++	+	—	—	—	—	—
Jan. 1	+++	+	+	—	—	—	—

In an effort to determine the rôle of complement and the thermolability of hemolysin, the following tubes were set up and subjected to 0° C. for 30 minutes and then to 37° C. for 30 minutes:

- (1) 0.5 c.c. patient's serum (separated from the clot after 12 hours at 37° C.)  
0.2 c.c. patient's RBC suspension (5 per cent)  
0.3 c.c. saline  
Results: Hemolysis.
- (2) 0.5 c.c. patient's serum (inactivated at 56° C. for 30 minutes)  
0.2 c.c. patient's RBC suspension (5 per cent)  
0.3 c.c. saline  
Results: No hemolysis.

- (3) 0.5 c.c. patient's serum (inactivated at 56° C. for 30 minutes)
- 0.2 c.c. patient's RBC suspension (5 per cent)
- 0.2 c.c. complement (1:10 guinea pig serum)
- 0.1 c.c. saline

Results: No hemolysis.

These experiments indicate that added complement is not essential to the *in vitro* hemolytic reaction and that the hemolysin is destroyed by subjecting it to a temperature of 56° C. for 30 minutes.

Studies were made to determine any relationship between cold hemagglutination and cold hemolysis. The Donath-Landsteiner procedure was carried out and at the end of 30 minutes at 0° C. no agglutination was observed, but at the end of an additional 30 minutes at 0° C. agglutination occurred. The agglutination became more marked after centrifugation. The tube was then shaken gently and allowed to remain at 0° C. overnight, during which time hemolysis occurred. Repetition of the procedure without added complement (guinea pig serum) failed to produce hemagglutination.

Following the method used by Stats and Wassermann,<sup>7</sup> in which they demonstrated *in vivo* cold agglutination, the patient was subjected to the following experiment: The conjunctival sacs were irrigated continuously for one and one-half minutes with 100 c.c. iced solution of normal saline and then immediately observed with the slit lamp. The flow of capillary blood was not seen to be interrupted by agglutination.

Having discovered the presence of cold autohemolysis by *in vitro* methods, experiments were performed to confirm its occurrence *in vivo*. The following qualitative test was conducted on October 9. Elastic band tourniquets were tightly applied around the bases of both fourth fingers. The right one was immersed in ice water at 4° C. for 10 minutes while the left one remained at room temperature (26° C.) for 10 minutes. With the tourniquets still in place both fourth fingers were immersed in a water bath at 37° C. for 10 minutes. Without releasing the tourniquets blood was drawn from the tips of both fingers into capillary tubes. One end of each tube was sealed, and the tubes were centrifuged. The serum from the right was red, indicating hemolysis (hemoglobinemia) occurring *in vivo*, whereas the serum from the left was colorless, indicating lack of hemolysis.

On October 12 the patient was subjected to the following experiment. Dressed in pajamas and robe of cotton and without other clothing, he was placed in a refrigerator at a temperature of 4.5° C. for 30 minutes beginning at 10:27 a.m. At 10:57 a.m. he was placed in a room at 20° C., and at 11:05 a.m. in a room at 29° C., where he remained for one hour, after which he returned to the ward. There was no further exposure to cold during the next 18 hours. Venous blood and urine specimens were taken at the times indicated in table 4, in which are presented the results of the experiment. Serum hemoglobin determinations were performed by the Army Medical Center in accordance with a modified spectrophotometric method described by Cohn.<sup>8</sup> Blood taken from the fingertip in the refrigerator at 10:57 a.m. showed no gross agglutination. Serum bilirubin determinations were not performed due to insufficient quantity of blood withdrawn.

Skin reaction to cold was studied by fixing ice in contact with the skin of the patient's back for 20 minutes (patch test). Inspection 20 minutes after removal of the ice revealed an erythematous, edematous, urticarial-like reaction, 3 cm. by 3 cm. in diameter. Using the same procedure, two Negro males were tested as controls, one a non-syphilitic who showed erythema with no edema, and the other a latent syphilitic who showed no reaction. Momentary contact of a small area of the patient's skin with ethyl chloride spray resulted in an epithelial necrosis, the site of which became pigmented after eventual healing occurred.

TABLE IV

Results of Serum and Urine Studies Following Exposure of the Patient to 4.5 C.° for 30 Minutes

Time	Appearance of Serum	Serum Hemoglobin	Serum Benzidine (positive in dilution of)	Urine Hemo-globin	Urine Urobilinogen
10:15 a.m.	Straw colored	16.0 mg. %	1:100 (++)	negative	negative
11:00 a.m.	Red	320.0 mg. %	1:100,000 (+)	negative	negative
11:15 a.m.	Reddish brown	136.0 mg. %	1:1000 (+)		
11:25 a.m.	Reddish brown	95.0 mg. %	1:1000 (++)		
11:35 a.m.	Amber	118.0 mg. %	1:1000 (+)		
11:45 a.m.	Amber	100.0 mg. %	1:1000 (++)	negative	negative
12:45 p.m.	Amber	121.0 mg. %	1:100 (++)	negative	negative
2:00 p.m.				negative	negative
3:00 p.m.	Pale pink	179.0 mg. %	1:1000 (++)	negative	positive 1:10
3:00 p.m.-6:00 p.m.				negative	positive 1:10
6:00 p.m.-6:00 a.m.				negative	positive 1:10

In an attempt to reproduce in a laboratory animal the vasospastic phenomena as observed in the patient, and as suggested by the work of Benians,<sup>10</sup> the following experiment was performed. Using light ether anesthesia, 1.0 c.c. of the patient's serum at 4° C. was injected into the right external carotid artery of a rabbit. By simple transillumination the vascular systems and the gross skin temperatures of the ears were observed for two hours after the injection, with no discernible difference between the two ears. The animal died 15 hours following the injection. At autopsy the lungs were extremely edematous, showing areas of hemorrhagic infiltration and pulmonary congestion. Histologically, the primary lesion consisted of marked edema of the walls of the arterioles, most apparent in the lungs and kidneys. This change was most pronounced in the muscularis of the arterioles, as evidenced by wide separation of the smooth muscle fibers, swelling of the sarcoplasm, and large, clear, easily visible nuclei.

### DISCUSSION

The serologic mechanism of paroxysmal hemoglobinuria due to cold is generally accepted to be a hemolytic system based upon an antigen-amboceptor-complement union, with the reaction occurring in two phases: (1) union of antigen (serum) and amboceptor (erythrocytes) only at low temperatures, and (2) lysis of the erythrocytes in the presence of complement on warming.

The antigen, hemolysin, is contained in the serum of the patient, as indicated by the absence of hemolysis when control serum was substituted for that of the patient in the Donath-Landsteiner reaction. In addition to autohemolysin, the patient's serum was shown to contain isohemolysin, which hemolyzed the red blood cells of another individual of the same blood group. Inactivation of the hemolysin resulted from exposure to 56° C. for 30 minutes, though the minimum inactivating temperature was not established. The lysis of one of Mackenzie's<sup>4</sup> patients was destroyed by 45° C. for 30 minutes and that of another by 47.5° C. for 30 minutes. Union of lysis and erythrocytes occurred at a maximum temperature of 8° C., and failed to occur at 14° C. However, temperatures of 4° C. and 0° C. apparently resulted in more complete union as indicated by hemolysis in higher dilutions of sera after warming. Union at considerably higher temperatures has been found by other observers (Donath and Landsteiner<sup>1</sup>). Con-

trary to the studies of Yorke and Macfie,<sup>1</sup> which indicated that greater hemolysis occurs after chilling for five to seven minutes than after chilling for 30 minutes, our experiment failed to produce hemolysis in any titer after exposure to 0° C. for only six minutes. Complement is an essential component of the hemolytic system, and its necessity is recognized by most investigators. The experiment performed in this case proves that there was sufficient complement in the patient's serum to effect hemolysis. Also, in another experiment, 56° C. for 30 minutes destroyed both lysin and complement, so that adding guinea pig complement failed to reactivate the hemolytic system. Myer and Emmerich<sup>1</sup> and others have found by quantitative methods that the repeated occurrence of clinical attacks of hemolysis reduces or even causes complete disappearance of complement from the serum, with at times the occurrence of anticomplementary properties in the serum. Considerable fluctuation in the titer of our patient's autohemolysin was found, and it is possible that the numerous clinical attacks which had occurred may have produced the weak Donath-Landsteiner reaction recorded on December 1.

The relationship of the lysin in syphilitic autohemolysis to the antigen giving rise to the positive Wassermann reaction is not clear, and experimental work has led to conflicting opinions. Mackenzie<sup>4</sup> has repeatedly removed the autolysin by absorption at low temperature by erythrocytes and found that the titer of the Wassermann reacting substance is not appreciably changed. Based upon his own and the experimental work of others he concludes that "syphilitic infection involves the liberation of antigens either from the spirochetes themselves or from the organs of the host or from both, which determine the production by the infected individual of antibodies of more than one type i.e., the autohemolysin and the Wassermann reagin. . . . Why some syphilitics develop the autohemolysin and others do not is quite obscure."

There is no proved relationship between paroxysmal hemoglobinuria of the syphilitic type and cold autohemagglutination, even when the latter is associated with hemoglobinuria. Both systems require chilling, but in hemagglutination, on warming the tube to 37° C., agglutinated red cells disperse without hemolysis. Occasional patients with hemagglutination also develop hemolysis and hemoglobinuria on exposure to cold, without the phenomenon being paralleled in vitro (Roth,<sup>9</sup> Stats and Bullowa<sup>11</sup>). In our case intravital agglutination could not be demonstrated, but after an excessive period of chilling of the patient's blood in the presence of added complement and after centrifugation hemagglutination occurred. This finding is believed to represent a coincidental and independent association in the same patient of a low titer of autohemagglutinins, such as occurs in most normal human sera, with a relatively high titer of autohemolysins.

There is basis for the concept that the Donath-Landsteiner reaction is a reproduction in vitro of the hemolytic reaction which takes place in the vascular system during an attack of hemoglobinuria. Exposure of this patient to 4.5° C. for 30 minutes produced sufficient chilling of the blood in the superficial capillaries to effect union of lysin with erythrocytes. It is safe to assume that on passing to the higher temperature of the interior of the body the second stage of the reaction, or hemolysis, took place. Jones<sup>12</sup> has proved that following an attack the hemoglobin is rapidly converted to bilirubin. Whether or not, therefore, hemoglobinuria occurs would depend upon the degree of hemoglobinemia, rapidity of conversion to bilirubin, and the threshold of the kidney for hemoglobin. The concentration of hemoglobin in the serum as a rule must reach 0.70 gm. per

cent before it appears in the urine.<sup>13</sup> The occurrence of attacks in this patient without apparent chilling, as in other cases reported, suggests that there may be an additional, though less important, factor in the hemolytic mechanism. Some investigators suggest that this secondary factor may be a variation in titer of the lysin, based on the observation of parallelism between attacks and lysin titers. No such parallelism was noted in this case.

The clinical syndrome of this disease varies markedly between patients, and between attacks in the same patient. As in this patient, attention is usually first called to the disease by passage of dark urine, ranging from dark brown to Burgundy red, depending upon the relative amounts of methemoglobin, oxyhemoglobin and hematin present. Passage of such urine is usually preceded by exposure to cold, but attacks may occur in warm weather. At the onset general symptoms may occur, including a chill, aching in the back and legs, headache, nausea, vomiting, malaise, and fever of two to four degrees F. These symptoms subside after several hours. Leukopenia usually occurs immediately after an attack, to be followed by leukocytosis. It is possible that in this case white blood counts were made too late to discover a transient leukopenia. Icterus of the hemolytic type has been noted a few days afterwards, and transitory enlargement of the spleen or liver has been reported. Anemia results from frequent severe attacks. Many patients with this disease may present only hemoglobinuria without systemic symptoms; others may experience general symptoms without passage of dark urine; and still others may present hemoglobinemia without any symptoms. Vasomotor symptoms, especially urticaria or Raynaud's syndrome, are of common occurrence during the attacks. In this patient pain in the fingers was common to all recorded attacks. Raynaud's syndrome occurred in three of five patients with this disease studied by Mackenzie.<sup>4</sup>

The pathogenesis of the vascular phenomena in syphilitic autohemolysis is unknown. Whether the mechanism involves the vasomotor system with resulting arteriolar spasm or whether there is a local obliterative arteritis, such as is known to occur in some cases of syphilis, has not been proved. Ischemic symptoms occurring with cold autohemagglutination are assumed to be due to occlusion of capillaries by agglutinated erythrocytes. Benians,<sup>10</sup> in an effort to determine the presence of a toxic factor in the serum of a patient with cold agglutination and Raynaud's syndrome, injected chilled serum of the patient into a rabbit, resulting in death of the animal, necropsy of which showed marked pulmonary edema. In our similar experiment, in which the chilled serum was placed into the arterial circulation, no local vascular phenomena were observed; however, the animal succumbed as a result of what appeared grossly to be the pathologic picture of shock. The microscopic changes observed in the arterioles, though suggesting an early arteriolitis, were not sufficiently specific to be conclusive or significant in linking the presence of cold autohemolysins with the vascular changes observed in these patients.

Treatment of this disease consists primarily of adequate treatment of the syphilis with which it is associated. This patient had received adequate bismuth and arsenical therapy prior to our observation. During the administration of penicillin, symptoms resembling those of a Herxheimer reaction occurred. The serological fastness to antisiphilitic therapy insofar as pertains to both types of antibodies, i.e., Wassermann reagin and autohemolysin, suggests a parallelism of failure of response to therapy. Mackenzie<sup>4</sup> states that in his five cases the rapid-



ity of fall of the lysin titer was roughly proportional to the intensity of treatment. These facts tend to indicate that the two types of antibodies, even though different in their behavior, may be released in visceral syphilis from the same antigenic source.

### SUMMARY

A case of syphilitic paroxysmal hemoglobinuria with Raynaud's syndrome is presented. The results of laboratory and experimental studies, with their interpretations and variations from other similar cases, are given. The serologic and biologic mechanisms of the disease are discussed with comment upon symptomatology and treatment.

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## EDITORIAL

### NEW DEVELOPMENTS IN THE MANAGEMENT OF LEPROSY

"GLIDER, parachute, submarine rescue, experimental diving, *handling of lepers*, demolition of explosives, observation flying." These categories were recommended for "Hazard Pay" by the Advisory Committee on Service Pay as recently as December 1948. When the justification for listing the demolition of explosives and the handling of lepers as comparable hazards was challenged, a spokesman of the committee defended the inclusion of leper handling on the grounds that hazard pay would compensate for "the fear of the disease felt by the average individual and the social stigma attendant to such service." This attitude is both an anachronism and a disgrace. As a comment on the "hazard" attaching to the handling of lepers it may be mentioned that in the 54 years since the National Leprosarium at Carville has been operating no member of medical or nursing staff has contracted the disease.

In the management of leprosy there are three departments—specific therapy, the treatment of complications, and the public health aspect of handling of the disease. It is perhaps in this last department that most progress has recently been made, although persistence of the biblical attitude in many quarters, as expressed by the Advisory Committee on Service Pay, is discouraging. However, leprologists are today united in their purpose to treat the disease on its merits and to reorient the attitude of doctors and the public towards it. Much has been accomplished, but much remains. Before the disease can be finally dealt with on an adequate and comprehensive scale public opinion *must* be altered. The fact that the Bible can be quoted in support of stringent measures for the control of leprosy remains a surprisingly important influence operating against a proper management of the problem. This supposed biblical authority is founded on the inaccurate supposition that biblical "leprosy" was leprosy as we know the disease. It clearly was not, and this must be publicized.

Elimination of the terms "leprosy" and "leper" is another important step. These words are irretrievably allied with social reproach. Not that there is anything sinister in their origin: they come from the adjective *λεπρός*, which simply means "rough" or "scaly." But by use they are associated with stigma from which they probably could never be divorced. Therefore the suggestion that *Hansen's disease* or *hansenosis*, or even *globiosis*, be adopted universally has much to be said for it. Even those who religiously deplore the conservation of eponyms should have little objection to this humane substitution.

Changes in the official attitude in the actual handling of patients with the disease are taking place. At worst, leprosy is less infectious than tuberculosis; often it is not infectious at all. The routine isolation of all

sufferers is therefore manifestly out of date. It is a hangover from the Middle Ages when the leper, thought to be cursed of God and a menace to mankind, was ruthlessly banished from human society and declared legally dead:

"Living corpses, they wandered to and fro, muffled from head to foot; a hood drawn over the face, and carrying in the hand a bell, the Lazarus-bell as it was called, through which they were to give timely warning of their approach" (Heine).

It is generally believed by leprologists today that lepromatous and "mixed" forms are alone possible sources of infection. The tuberculoid type, unfortunately the rarest and most benign, is probably not infectious. Cases of all types which have reached a stage of arrest should be regarded as non-communicable, though the possibility of relapse must always be remembered. Norwegian health authorities have struck the right note in emphasizing the isolation of cases regarded as communicable, rather than all cases regardless of clinical type. McCoy<sup>1</sup> in this country recommends that cases should be considered to fall into three groups:

- (a) Those that require care in special hospitals—communicable cases in areas where spread is likely to occur, i.e. in endemic areas of Louisiana, Texas, Florida, and, to a less extent, California.
- (b) Those that require isolation at home or in a general hospital—this covers all types of cases in areas where transmission is unlikely, i.e. all states besides those listed under (a).
- (c) Those that require no special consideration—non-communicable cases in areas where transmission is unlikely.

These principles, as enunciated by McCoy, are generally acceptable—isolation is needed only in bacteriologically positive cases and in endemic areas, particularly where hygienic conditions are primitive and intelligence low. Children, who are particularly susceptible, must of course be protected, and babies born to leprous parents should be removed from them immediately.

Rogers,<sup>2</sup> with his wide experience in the British Empire, has much the same general opinion. Austin,<sup>3</sup> however, from his rather unique position in Fiji, rightly cautions that medical policy should be determined in the light of local circumstance and not by rule of thumb. It seems likely that in certain native areas compulsory isolation may remain a *sine qua non* of efficacious treatment.

Meanwhile, at the National Leprosarium, three highly significant events occurred in 1948. In July, for the first time, a patient received a medical discharge while still in the "communicable" stage of the disease. Such discharges may now be authorized if a physician has indicated his willingness

<sup>1</sup> McCoy, G. W.: Factors in public health management of leprosy, Pub. Health Rep., 1948, lxiii, 1522.

<sup>2</sup> ROGERS, SIR LEONARD: Progress in the control of leprosy in the British Empire, British Med. Jr., 1946, i, 825.

<sup>3</sup> AUSTIN, C. J.: Correspondence, British Med. Jr., 1947, i, 506.

to provide continuous treatment, to make monthly reports on the patient's progress and to observe the patient's home conditions; if the patient's family is financially able to pay continuing costs of proper treatment; if there are no children and few adults in the home; and if the state health officer is notified of the conditions of discharge and concurs in the proposed disposition of the patient. The second event took place the following month and was symbolic—in the words of one of the patients who has been at Carville for nearly twenty years—symbolic of the gradual change “from almost a penal institution to almost a modern hospital”: the barbed wire was removed from the top of the high fence in front of the hospital. Then in October a patient was discharged as an “arrested” case after only *six* consecutive negative bacterial examinations, instead of the previously routine twelve.

These changes do not represent a slackening of sensible precautions, but rather a belated revision of medieval principles. They show that the Public Health Service is rightly acting in accordance with both scientific knowledge and human feeling. Disease is not a crime punishable by imprisonment, and there is no reason why Hansen's disease alone should be governed by an Erewhonian legislative. If the disease as a whole is to be most effectively handled the Public Health Service must increase the momentum of its activities in many directions, always aiming primarily at an educated public opinion, without which any scheme for its control is foredoomed to failure. All must be educated to regard it as a disease to be feared less than many others and one to which no stigma attaches; the revision of attitude on the part of the authorities in handling the disease, as well as current advances in chemotherapy, must be widely publicized. Doctors, especially in endemic areas, must be trained to recognize the disease. Only when such an educational program reaches fruition will the maximum number of cases be exposed to the most effective available therapy.

While the reëvaluation of our attitude may represent the most significant advance in the management of Hansen's disease, specific therapy has not lagged far behind. Chaulmoogra oil, the time-honored remedy, in use at least since the days when the Burmese King, Rama, cured himself and his jungle sweetheart with the fruit of the Kalow Tree, has recently fallen into partial disrepute. Newer remedies have been hailed as more effective and less toxic. But the evidence available must be closely scrutinized, and more must be accumulated, before final judgment is passed. It has been said<sup>4</sup> that no one has yet carried out a proper test for the efficacy of chaulmoogra. It is interesting to notice how the pendulum of opinion has swung. A quarter of a century ago responsible British authorities were so optimistic that they stated that leprosy should be eliminated from the Empire within 30 years. In 1938 the International Leprosy Congress stated,<sup>5</sup> “Chaulmoogra oil from the *Hydnocarpus* species, and its ethyl esters, remains the most efficacious agent for the special treatment of Leprosy.” In 1941 a team of

<sup>4</sup> GRAY, H.: The chemotherapy of leprosy, *New Orleans Med. and Surg. Jr.*, 1947, c, 218.

<sup>5</sup> International Leprosy Congress Report 1938, *Internat. Jr. Leprosy*, 1938, vi, 408.

recognized therapeutists were able to write "with the development of the improved methods for the use of this drug, the outlook of the leper has changed from one of a lifetime of segregation to a reasonable expectancy of a complete cure."<sup>6</sup> Then McCoy,<sup>7</sup> in the following year, stated that twenty-five years of personal observation had left him with the very definite impression that chaulmoogra oil and its derivatives were of doubtful value in the treatment of leprosy. In 1948, another therapeutic team,<sup>8</sup> no less distinguished than the first, stated, with apparently no note of equivocation in their voices, that the oil is "absolutely of no value in treatment." That, however, is undoubtedly going too far. Fite<sup>9</sup> sums up the present status of chaulmoogra therapy impartially and well as consisting of disparaging critical opinions on the part of those who have used it comparatively little, opposed by favorable reports from those who have used it extensively in the absence of a better therapeutic agent. Certainly many authorities outside the United States (and only 0.1 per cent of the world's lepers are in this country) consider chaulmoogra oil to be of real benefit. Schujman<sup>10</sup> emphasizes that the success of hydnocarpus therapy is largely dependent on the dosage and the method of administration. He states that any method which does not include *intradermal* injections, or in which the patient receives a total of less than 400 c.c. in a year, is likely to bring these drugs into disrepute. Cochrane<sup>11</sup> heartily agrees. At the 1948 International Leprosy Congress it was said to be increasingly evident that greatest benefit results from high dosage (15 to 25 c.c. weekly), given regularly, and divided between the subcutaneous, intramuscular and intradermal routes; and that maximal doses should be attained as quickly as possible.<sup>12</sup>

It may well be that racial and other factors influence the effectiveness of chaulmoogra. Thus Cochrane claims better results in Indians with chaulmoogra than with sulfones; they appear to respond better to hydnocarpus than Europeans, and they also appear to be more easily intoxicated with sulfones. As recently as April 1948, Schujman in Argentina<sup>13</sup> questions whether chaulmoogra or the sulfones are more effective. In two small series of comparable lepromatous cases, one on chaulmoogra and one on sulfone therapy, similar improvement was seen in each series after 18 months' treatment.

<sup>6</sup> GOODMAN, L., and GILMAN, A.: *The Pharmacological Basis of Therapeutics*, 1941, The Macmillan Co., N. Y., p. 944.

<sup>7</sup> MCCOY, G. W.: Chaulmoogra oil in treatment of leprosy, *Pub. Health Rep.*, 1942, lvii, 1727.

<sup>8</sup> REHFUSS, M. E., ALBRECHT, F. K., and PRICE, A. H.: *A Course in Practical Therapeutics*, 1948, The Williams & Wilkins Co., Baltimore, p. 529.

<sup>9</sup> FITE, G. L.: Leprosy, its detection and management, *Postgraduate Med.*, 1947, i, 292.

<sup>10</sup> SCHUJMAN, S.: Therapeutic value of chaulmoogra in the treatment of leprosy, *Internat. Jr. Leprosy*, 1947, xv, 135.

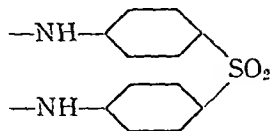
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<sup>13</sup> SCHUJMAN, S.: Comparative study of chaulmoogra in high doses and promin in the treatment of leprosy, *Internat. Jr. Leprosy*, 1948, xvi, 145.

Chaulmoogra is not, therefore, simply dying unsung. Though all admit it is a far from satisfactory answer to the problem of Hansen's disease, it is apparently, in the opinion of those who know it best, not as useless as some authors indicate. At the moment, however, the spotlight of therapy is sharply focused on the sulfones.

Diaminodiphenyl sulfone is the parent radicle and the active principle of the sulfones. It was first synthesized in 1908,<sup>14</sup> and its chemical formula is as follows:



Those of its derivatives which have been used to any extent in leprosy are:

1. Promin (called promanide in Britain); the sodium salt of diaminodiphenyl sulfone-N,N'-didextrose sulfonate.
2. Diasone (Abbott), diamidin (Parke Davis); disodium formaldehyde sulfoxylate of diaminodiphenyl sulfone.
3. Promizole; 4,2' diaminophenyl-5-thiazolylsulfone.
4. Sulphetrone (a British drug); tetrasodium phenylpropyl aminodiphenyl-sulfone tetrasulphonate.

The first indication that the sulfones had an antibacterial action came in 1937 from British workers<sup>15</sup> treating experimental streptococcal infections in mice. They found promin to be 100 per cent more effective than sulfanilamide. Later it was used in experimental tuberculosis<sup>16</sup> with encouraging results, and in rat leprosy<sup>17</sup> with less spectacular effect, although some curative action was demonstrated. Finally, in 1941, the first cases of human leprosy were treated with promin at Carville. Faget and his colleagues<sup>18</sup> made a heartening preliminary report in 1943, when they described their clinical trial of promin as "the most encouraging experimental treatment ever undertaken" at the National Leprosarium. Meanwhile Muir<sup>19</sup> initiated a clinical trial with diasone in Trinidad. This drug has been used at Carville since 1943.<sup>20</sup> Investigations with promizole at Carville and sulphetrone in India have been instituted more recently.

<sup>14</sup> FROMM, E., and WITTMANN, J.: Derivate des p-nitrophenols, Ber. d. deutsch. chem. Gesellsch., 1908, xli, 2264.

<sup>15</sup> BUTTLE, G. A. H., et al.: Treatment of streptococcal infections in mice with 4-4'-diaminodiphenylsulphone, Lancet, 1937, i, 1331.

<sup>16</sup> FELDMAN, W. H., et al.: The treatment of experimental tuberculosis with promin; a preliminary report, Proc. Staff. Meet. Mayo Clin., 1941, xvi, 187.

<sup>17</sup> COWDRY, E. V., and RUANGSIRI, C.: Influence of promin, starch and hepatalhyde on experimental leprosy in rats, Arch. Path., 1941, xxxii, 632.

<sup>18</sup> FAGET, G. H., et al.: The promin treatment of leprosy: a progress report, Pub. Health Rep., 1943, lviii, 1729.

<sup>19</sup> MUIR, E.: Preliminary report on diasone in treatment of leprosy, Internat. Jr. Leprosy, 1944, xii, 1.

<sup>20</sup> FAGET, G. H., et al.: The action of diasone in the treatment of leprosy, preliminary report, Internat. Jr. Leprosy, 1946, xiv, 19.

As far as can be judged at this stage all the sulfones so far used have a comparable therapeutic effect. Faget and Erickson<sup>21</sup> have reported their results in 317 patients treated with promin or diasone. Of 178 treated with promin for up to six years, 31 (17.4 per cent) have been discharged as "arrested"; of 121 treated with diasone for up to four years, 7 (5.8 per cent) have become "arrested." Of the remaining 18, treated with both drugs at one time or another, none have yet been "arrested." In the authors' opinion the apparently better results with promin are almost certainly due to the fact that *more* patients have received promin *longer*. Time is undoubtedly an all important factor. In Fite's words<sup>8</sup> leprosy is a "fiercely chronic affair," and impatience certainly has no place in evaluating methods of therapy in Hansen's disease.

In scanning these authors' statistics two points are noticeable: first, of all those patients treated for at least three years (89), over 25 per cent (23) have become arrested. Second, 92 of the 317 patients had been under treatment for less than one year, and are immediately, therefore, disqualified from the possibility of being considered arrested—one of the criteria for arrest being *twelve* consecutive months of negative bacterioscopy.

Examining the relationship of response to duration of treatment from another point of view the authors claim that "some objective improvement" is shown by almost 25 per cent of cases after six months, by 60 per cent after one year, by 75 per cent after two years, and by nearly 100 per cent after three years. They further claim that the stage of disease reached does not prejudice the action of these drugs, and that even far advanced hansenosis is checked and improves under treatment. Improvement in the individual, however, varies proportionately with the size of dose tolerated by that individual. During 1946 the number of cases discharged from the National Leprosarium with arrested disease more than doubled the annual average for the 10 years prior to the use of the sulfones, and the number of deaths during the year was less than half the annual average.

Another impressive series is reported by Lima<sup>22</sup> who has treated 1287 cases in Brazil during the past four and one half years. Of these, 847 were lepromatous and were treated from one to three years. Of 584 advanced cases, complete disappearance of skin lesions occurred in 46 cases (8 per cent), "marked improvement" took place in 143 (24 per cent), lesser degrees of improvement in 373 (64 per cent), while only 22 (4 per cent) were unaltered. He found that in only moderately advanced and "incipient" cases the percentage, in whom improvement occurred, was proportionately greater; thus, of 99 incipient cases 67 per cent cleared completely, while *all* the rest showed definite improvement.

<sup>21</sup> FAGET, G. H., and ERICKSON, P. T.: Chemotherapy of leprosy, Jr. Am. Med. Assoc., 1948, cxxxvi, 451.

<sup>22</sup> LIMA, L. DE S.: Present status of sulfone therapy at the Padre Bento Sanatorium, Internat. Jr. Leprosy, 1948, xvi, 127.

Favorable results of sulfone treatment have also been reported from Hawaii, Argentina, Costa Rica, Cuba, British West Indies, British Guiana, India and Africa.

Objective improvement is shown in many ways. Mucosal lesions respond more rapidly than cutaneous. Oral nodules and infiltrations subside and disappear within a few months, nasal obstruction is relieved, and tracheotomies become generally unnecessary. Sloan<sup>23</sup> considers that "improvement in laryngeal lesions is one of the most striking results of sulfone treatment, perhaps *the* most striking one." In the skin small nodular lesions shrink to complete absorption leaving only a pigmented spot, while larger lesions disperse with scar formation. Ulcers gradually form healthy granulations and heal through cicatrix formation. Occasionally regrowth of hair—in eyebrows, beard and on limbs—follows resolution of lepromatous lesions. Bacteriological response is more leisurely. During the first year of treatment practically all cases retain positive skin and nasal smears; after four years of continuous treatment, however, the incidence of negative reports exceeds 50 per cent. Fite<sup>9</sup> believes that the sulfones dispose of the lesions of the small blood vessels in the leprous granulomas "which are forever casting bacilli into the blood stream." With this as the assumed basis of their action he sums up the effect of treatment as follows: patients are largely freed from the risk of acute reactions; the appearance of new lesions is greatly cut down, and eliminated in the majority of cases; secondary infections are virtually absent. "Under these conditions the opportunity for the lesions to atrophy and regress is greatly enhanced, and this is precisely what takes place, at about the same rate as in examples of spontaneous regression without treatment." Acute lepra reactions with erythema nodosum or erysipeloid dermatitis are not commonly aborted by sulfone therapy. Recurrences, in fact, may occur during therapy, but their frequency and severity are lessened.

Apart from objective improvement the great majority of patients develop a sense of well being, have more energy, sleep better, and in general feel they have a new lease on life. A gain of weight is apparently universal.

Promin was at first given orally, but it was soon found that in adequate dosage it was too toxic by this route, and so it was administered intravenously. Used in this way it has proved much more tolerable. It is too early to say finally what the optimal dose of any of the sulfones is, but the recommended dose of promin, as accepted at the International Leprosy Congress in 1948,<sup>12</sup> is 5 grams daily for one to three months, followed by a rest period of one to two weeks.

Diasone has the great advantage of being well tolerated by mouth: its recommended dose is up to a maximum of 1.8 grams daily, with a rest of one to two weeks every two months. The dose usually employed so far, however, has been 0.9 gram daily. Diasone also has the virtue of being

<sup>23</sup> SLOAN, N. R.: Effect of sulfone treatment on the larynx in leprosy, *Internat. Jr. Leprosy*, 1948, xvi, 329.



comparatively inexpensive: it has been calculated that the cost of one year's supply for one patient is \$21.60, and at Carville it has been found that the saving in dressings, since the advent of sulfone therapy, pays the whole cost of the new medicine.

The use of promizole was begun at Carville in 1945: the dosage employed was much larger than that for diasone, 6 to 8 grams being given daily by mouth, with a rest period of two weeks every two months. Although it appeared to be as active therapeutically as the other sulfones, its use has since been discontinued because difficulty of manufacture increases its cost to a point which limits its usefulness.

Sulphetrone is recommended in a daily dosage of 3 to 6 grams orally, continued for six months, when a rest period, its duration dictated by individual tolerance, is allowed. With all the sulfones it is recommended that a smaller initial dose be used, with gradual increase to the optimal in the course of the first few weeks.

The sulfones have their disadvantages. They are toxic to erythrocytes, causing a slowly developing hemolytic anemia. This anemia can usually be modified by iron therapy, however. Leukopenia occasionally occurs, and one death from agranulocytosis, for which diasone was blamed, has been mentioned as having occurred in Hawaii.<sup>24</sup> Allergic dermatitis is an infrequent complication. Nausea, vomiting, and headache sometimes develop but are never severe. An attack of sneezing frequently follows the injection of promin. Hematuria, without crystalluria, occurred in a few cases on high initial dosage of diasone; gastric irritation and fever were also occasionally caused. Cochrane<sup>25</sup> found sulphetrone to be the least toxic preparation to Indians. He dismisses promin as "too toxic for ordinary use," and finds that diasone "is very liable to set up lepra reactions, frequently extremely severe"; 14 of 22 cases suffered from such reactions.

As each new chemotherapeutic and antibiotic agent appears on the scene it is, of course, tried in Hansen's disease. Faget and his colleagues found sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine to be ineffective. Penicillin has likewise been tried and found wanting. Both penicillin and the sulfonamides, however, have been found of value in controlling the secondary infections of leprous ulcerations. Streptomycin, as might be expected, has appeared more promising.<sup>21</sup> In eight lepromatous cases at Carville 2 grams were administered by intramuscular injection daily for four months: thereafter the dose was reduced to 1 gram because of severe toxic reactions. Encouraging changes seemed to occur in mucosal and cutaneous lesions in some cases during the first three months of therapy; but after this initial response, improvement was not maintained, suggesting the develop-

<sup>24</sup> JOHNSON, H. M.: Discussion following Faget and Erickson's paper.<sup>21</sup>

<sup>25</sup> COCHRANE, R. G.: Correspondence, *Brit. Med. Jr.*, 1947, ii, 110.

<sup>26</sup> HINGSON, R. A., et al.: Preliminary study of the hypospray for parenteral therapy in its relation to the management of leprosy, *Internat. Jr. Leprosy*, 1948, xvi, 173.

<sup>27</sup> MOM, M.: Benadryl in lepra reaction of lepromatous leprosy and in sulfone sensitization, *Rev. argent. dermatosif.*, 1947, xxxi, No. 2.

ment of bacterial resistance. It seems likely that the value of streptomycin in Hansen's disease will be limited by its toxicity and the likely development of bacterial resistance. Used locally in wet dressings, however, it has proved to be of some value in promoting the healing of leprosy lesions.

It is evident that in the last few years the study of leprosy has received great impetus and made great strides. The use of the sulfones with such striking results has naturally attracted most attention. But it is well to remember that the path of leprosy in the past half century is strewn with the wrecks of so-called "cures." In the case of the sulfones, however, confidence may be felt in the fact that so many experienced workers in so many parts of the world have obtained favorable results such as they have never before achieved with other remedies. What may, perhaps, be felt with even greater confidence and satisfaction is that we have taken irretraceable steps towards removing a longstanding reproach to our humane profession. It may well be hoped, therefore, that, with our recent progress both in attitude and in chemotherapy, we have at last closed the darkest chapter in the handling of leprosy, about which Burns might so well have written his melancholy alliteration,

Man's inhumanity to man  
Makes countless thousands mourn.

H. J. L. M.

## REVIEWS

*Hematology.* By CYRUS C. STURGIS, M.D., 915 pages; 17 × 26 cm. Charles C. Thomas, Springfield, Illinois. 1948. Price, \$12.50.

Since the turn of this century, no sub-specialty within the field of internal medicine has developed more rapidly than hematology, nor in any specialty have the results of both basic and clinical research been applied more specifically and gratifyingly. Following Ehrlich's discovery of the applicability of dyes to the differentiation and identification of the blood cells, cytologists concentrated on atlases delineating the minutest morphological cellular detail, resulting in more confusion than understanding for the physician. More recent decades have seen physiologists and clinicians clarifying this nomenclature-laden atmosphere, until now it is possible to translate a detailed history, discriminatory physical findings and selected laboratory data from the individual patient into an exact diagnosis from which logically and inevitably stems specific therapy.

All recent texts on the blood diseases have reflected this changing emphasis, and the University of Michigan's Dr. Sturgis, Director of the Simpson Memorial Institute for the study of pernicious anemia, has now written, out of his years of accumulated personal experience, the most recent practical review of this great field of medicine. Today's student of modern hematologic practice will find prompt orientation here, through a careful documentation of the more important scientific steps which have led to current concepts and practice. The great variety of anemic states, the hemorrhagic diatheses, the nature and character of the white cell dyscrasias, polycythemia and the lipoidoses are treated individually in detail in this order. Appropriate illustrative case histories, graphs and beautifully reproduced colored plates of representative "cellular pictures" of specific diseases are introduced where they are most effective. The great importance and applicability of experimental nutritional studies are effectively emphasized in discussing the clinical treatment of anemia patients.

The incidence, diagnosis, etiology, pathologic physiology, treatment, prognosis and complications are sub-headings for every disease entity, which make available for ready reference the breadth and variety of current hematologic knowledge. Chapters on sternal puncture and a very complete discussion of the indications for blood transfusion and the use of blood derivatives and blood substitutes complete this volume.

While it is true that hematology has become recognized as a subspecialty within the general field of internal medicine, it is also true that no physician, be he general practitioner, surgeon, or other specialist, can hope to practice good medicine today, without possessing much of the knowledge which has been learned by hematologic investigators in this domain of the bone marrow, spleen, liver and lymph nodes. The blood and blood cells are affected by everything we do and experience, as well as by our sins of omission. Most of the facts in Dr. Sturgis' volume on *Hematology*, therefore, are essential to all physicians in the best interest of the most complete and comprehensive care of their patients.

CHARLES A. DOAN, M.D.

*Clinical Aspects and Treatment of Surgical Infections.* By FRANK L. MELENEY, M.D., F.A.C.S. 840 pages, with 287 figures. 25 × 17 cm. W. B. Saunders Company, Philadelphia. 1949. Price, \$12.00.

The author describes himself as "a doctor who felt impelled to write a book." We can be thankful for that impulsion. Dr. Meleney has produced no ordinary book; he has plenty to say, and he says it well.

He is a pioneer in establishing the importance of a bacteriological laboratory closely integrated with a surgical service, and he believes that only by such integration can quickest healing and minimal disability be achieved. He writes from his own intimate knowledge gained through a wide experience of more than 25 years.

A good introductory chapter by Dr. John S. Lockwood on Physiological Considerations in Surgical Infections is followed by a series of 15 chapters each devoted to the surgical infections of an area, organ, or system of the body: Skin and Subcutaneous Tissues; Head and Neck; Heart, Pericardium and Mediastinum; Lungs and Pleura; Peritoneum (by Dr. Harold D. Harvey); Liver, Pancreas and Spleen; Gall-bladder and Bile Passages; Stomach and Small Intestine; Appendix; Colon; Genital and Urinary Tracts; Bones and Joints; Hand; Lower Extremity; Central Nervous System. Surgical Septicemia is then taken up; and in the final, eighteenth chapter War Wounds are discussed by Dr. Alfred B. Longacre and Dr. William R. Sandusky.

The format is excellent. The many illustrations are clear and helpful. Each subject is comprehensively discussed with particular emphasis on pathogenesis, bacteriology, and treatment. Each is amply illustrated with case histories which are well chosen and exemplify points of discussion in the text. These case reports are, as usual, given in somewhat smaller print, but the author employs the excellent device of adding, in the larger print of the general text, a resumé of the case at the conclusion of each report; thus it is made easy for the reader to select those case reports which illustrate a point of special interest to him. For his bibliography the author has culled widely the best of both American and British publications; nearly 1200 references document the text.

The importance of routine anaerobic as well as aerobic cultures is emphasized. Besides the Big Three in antibacterial warfare—the sulfonamides, penicillin, and streptomycin—the author makes considerable use of bacitracin and zinc peroxide. Bacitracin, which was discovered in his own laboratory, is particularly useful in Gram-positive infections which are not responsive to penicillin. Zinc peroxide, of course, finds its chief use in the control of anaerobic infections by topical application.

For anyone who has seen a carbuncle yield to systemic penicillin, it is hard to sympathize with the dictum “systemic administration is unnecessary and wasteful.” A carbuncle is surely one of the most clear-cut and unexceptionable indications for systemic penicillin. Moreover, the dosage in the illustrative cases in which it was so used was only 10,000 units every three hours. We cannot help wondering if this section was written some time ago and not since revised. It is surprising that in the clinical description of bronchiectasis clubbing of the fingers is not accorded even a passing mention.

But our only real regret is that the word “Surgical” appears, as indeed it must, in the title. As a titular word, it is one which the internist tends instinctively to avoid. Yet, with the division between surgery and internal medicine artificial as it is, there is something of interest and value to specialists in both fields in almost every chapter; for example, the accounts of bronchiectasis and of chronic ulcerative colitis, the discussion on the early recognition of acute hemolytic streptococcal gangrene, and that on the treatment of tetanus. These are just a few of the available instances of overlapping interest.

A well written, well published and remarkably detailed work, this book contains a wealth of practical up-to-date information. It represents a substantial contribution to surgery, bacteriology and medicine.

H. J. L. M.

*Handbook of Communicable Diseases.* 2nd Ed. By FRANKLIN H. TOP, A.B., M.D., M.P.H., F.A.C.P. 992 pages; 22.5 × 14.5 cm. 1947. The C. V. Mosby Company, Saint Louis. Price, \$9.50.

This second edition of a standard textbook on communicable diseases covers a very wide diversity of subjects, for it includes parasitic infections such as malaria and hookworm, virus and rickettsial infections of all varieties, bacterial infections including predominantly exotic diseases such as leprosy, all of the common venereal diseases, and several special infections such as epidemic diarrhea of the newborn, and epidemic kerato-conjunctivitis. Included also are a number of fungus diseases. To have all of this in one book, which has some 896 pages of text, is of course a worthy ideal but tends to produce a certain diffuseness. Dr. Top attempts to overcome this by having a number of authorities on special infections contribute to the edition:—Abernethy writes on Primary Atypical Pneumonia; Coggeshall on Malaria; Francis on Infectious Hepatitis; J. C. Snyder on Rickettsial Diseases, to mention a few. This adds considerable weight to the whole presentation.

All of this probably accounts for the number of debatable points in the book. The summary of the use of influenza vaccine (p. 95), although correct in its interpretation of the value of that vaccine as of two years ago, is no longer correct. Recent studies show that present vaccines are of no value against contemporary strains.

The chapter on the care and management of communicable disease in a hospital is so completely detailed that it loses any real power. The use of sulfadiazine as an effective agent in diarrhea of the newborn is a little misleading. In the discussion of encephalitis: Borna disease is not the same as equine encephalomyelitis. Outbreaks of this latter infection in man are probably not affected at all by control of the disease in horses, for all the available epidemiological evidence indicates that both man and horse are infected by mosquitoes which derive *their* infection from an avian reservoir host.

The book is superbly illustrated with a number of color plates, has a full bibliography at the end of each chapter. It will continue to be a valuable reference for those interested in infectious disease but cannot be considered as a final authority.

F. B. B.

*Diseases of the Chest, Described for Students and Practitioners.* 2nd Ed. By ROBERT COOPE, with a Foreword by LORD HORDER. 541 pages; 22.5 × 14.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$7.50.

The author of this text for students and practitioners has carried out admirably an almost impossible task—the condensation in a moderate sized volume of the physical diagnosis, symptoms, pathogenesis, etiology, symptomatic and chemotherapeutic treatment of almost any disease which affects the lungs.

This is done in a concise, didactic style in which the decision is already made for the student as to the cause and cure of the different diseases. There are no references at the end of the chapters which might allow the reader to pursue a more complete analysis of the subject. This does not mean that the book is not thorough. It is.

However, the size of the task perhaps is the cause of such omissions as the lack of mention of the use of streptomycin in the treatment of tularemia, or the brief consideration of influenza, in which it is assumed that the severe pandemic and the mild epidemic influenzas are the same disease.

It is, then, a clear presentation of one experienced man's distilled knowledge of the subject, but does not stimulate investigation of other sources of knowledge.

F. B. B.

*Synopsis of Pediatrics.* By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., assisted by T. S. ZAHORSKY, B.S., M.D. 449 pages; 13 × 20 cm. C. V. Mosby Co., St. Louis, Missouri. 1948. Price, \$5.50.

This is the fifth revision of a pediatric manual intended primarily for students. The present edition has been enlarged and newer advances in therapeutics have been included. There are a number of excellent color plates presenting the characteristic features of the various exanthems. However, as in all condensations of extensive subjects, the achievement of brevity is at the sacrifice of basic understanding.

J. E. B.

*Intestinal Obstructions.* 2nd Ed. By OWEN H. WANGENSTEEN, B.A., M.D., Ph.D. 484 pages; 17 × 25.5 cm. Charles C. Thomas, Springfield, Illinois. 1942. Price, \$7.00.

This is an extremely comprehensive book, dealing with the problem of intestinal obstruction. It is presented under four general parts or sections: Part 1 deals with the effects of obstruction, from the physiological and clinical viewpoint; Part 2 discusses general diagnostic considerations in bowel obstruction; Part 3 is devoted to general therapeutic considerations; and Part 4 to special obstructions. Each section is subdivided into appropriate subheads.

The author has included much that is of interest from the physiopathological viewpoint. Nevertheless, he has closely adhered to his original intention, and that is the development of a comprehensive and, at the same time, practical reference dealing with the problem of intestinal obstruction.

The book is well indexed, and contains an excellent author index as well as bibliography. The illustrations are excellent. The operative procedures are concisely described.

In summary, Dr. Wangensteen's monograph is an excellent reference from the diagnostic viewpoint as well as from the viewpoint of practical therapeutics.

G. H. Y.

### BOOKS RECEIVED

Books received for January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Blood Transfusion.* By ELMER L. DEGOWIN, M.D., Associate Professor of Internal Medicine, State University of Iowa, etc.; ROBERT C. HARDIN, M.D., Assistant Professor of Internal Medicine, State University of Iowa, etc.; and JOHN B. ELSEVER, M.D., Senior Surgeon, U. S. Public Health Service, etc. 587 pages; 24 × 16 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$9.00.

*The Business Side of Medical Practice.* 2nd Ed. By THEODORE WIPRUD, Executive Director and Secretary of The Medical Society of The District of Columbia and Managing Editor of the Medical Annals of the District of Columbia. 232 pages; 20.5 × 14 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$3.50.

*Cardiology.* By WILLIAM EVANS, M.D., D.Sc., F.R.C.P., Physician to the Cardiac Department of the London Hospital, etc. 330 pages; 25 × 17.5 cm. 1948. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$7.50.

- Clinical Aspects and Treatment of Surgical Infections.* By FRANK LAMONT MELENEY, M.D., F.A.C.S., Associate Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University, etc.; with a Foreword by ALLEN O. WHIPPLE, M.D. 840 pages; 25 × 17 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$12.00.
- Clinical Endocrinology for Practitioners and Students.* By LAURENCE MARTIN, M.D. (Camb.), F.R.C.P. (Lond.), Physician to Addenbrooke's Hospital, Cambridge, and MARTIN HYNES, M.D. (Camb.), M.R.C.P. (Lond.), Reader in Medicine in the University of Cambridge; with a Foreword by SIR LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P., D.P.H., Regius Professor of Physic, University of Cambridge. 222 pages; 22.5 × 14.5 cm. 1949. The Blakiston Company, Philadelphia. Price, \$4.50.
- Introduction to Physical Biochemistry.* 2nd Ed. By J. M. JOHLIN, Ph.D., D.Sc., Associate Professor of Biochemistry in the Vanderbilt University School of Medicine. 246 pages; 24 × 16 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$3.75.
- Lung Dust Lesions versus Tuberculosis.* By LEWIS GREGORY COLE, M.D., F.A.C.R. 474 pages; 27.5 × 20 cm. 1948. American Medical Films, Inc., White Plains, New York. Price, \$10.00.
- Manual of Clinical Laboratory Methods.* 4th Ed. By OPAL E. HEPLER, Ph.D., M.D., Associate Professor of Pathology, Northwestern University Medical School, etc.; with a Foreword by JAMES P. SIMONDS, Ph.D., M.D. 387 pages; 28 × 20.5 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$8.50.
- Mayo Clinic Diet Manual.* By THE COMMITTEE ON DIETETICS OF THE MAYO CLINIC. 329 pages; 24 × 16.5 cm. (paper-bound, loose-leaf). 1949. W. B. Saunders Company, Philadelphia. Price, \$4.00.
- Modern Trends in Psychological Medicine—1948.* Edited by NOEL G. HARRIS, M.D., F.R.C.P., D.P.M., Physician for Psychological Medicine, Middlesex Hospital, etc. 450 pages; 25 × 17.5 cm. 1948. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$10.00.
- Obstetric Analgesia and Anesthesia: Their Effects upon Labor and the Child.* By FRANKLIN F. SNYDER, M.D., Associate Professor of Obstetrics and Associate Professor of Anatomy, Harvard Medical School. 401 pages; 24 × 16 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$6.50.
- Oxford Loose-Leaf Medicine—Reprints of 21 Articles Published Recently as a Supplement.* 25 × 18 cm. 1948. Oxford University Press, Inc., New York. Material supplied only to subscribers to this work.
- Recent Advances in Respiratory Tuberculosis—4th Ed.* By FREDERICK HEAF, M.A., M.D., F.R.C.P., Senior Medical Officer, London County Council, etc., and N. LLOYD RUSBY, M.A., D.M., F.R.C.P., Assistant Physician, The London Hospital, etc. 290 pages; 21 × 14 cm. 1948. The Blakiston Company, Philadelphia. Price, \$5.50.
- Síndrome Anémico do Kala-azar.* By DR. CARLOS PINTO TRINCÃO. 68 pages; 25 × 17.5 cm. (paper-bound). 1948. Sociedade Industrial de Tipografia, Lisboa, Portugal.
- Veterans Administration Technical Bulletins, Series 10, 1946 and 1947.* 252 pages; 27 × 20.5 cm. January, 1948. Veterans Administration, Washington, D. C. Not for sale—limited edition for distribution to VA hospitals.

## COLLEGE NEWS NOTES

### POSTGRADUATE COURSES OFFERED BY THE AMERICAN COLLEGE OF PHYSICIANS

Already concluded on the spring schedule are courses in "Medical Aspects of Nuclear Energy" at the U. S. Army Medical Center, Washington; "Gastro-enterology" at Stamford University and the University of California, San Francisco; "Clinical Medicine from the Hematologic Viewpoint" at Ohio State University, Columbus; and "Internal Medicine" at the Massachusetts General Hospital, Boston.

Yet remaining on the spring schedule are the following courses:

- No. 5—**ELECTROCARDIOGRAPHY**; Massachusetts General Hospital, Boston, Mass.; 1 week, April 25-30; \$60.00, A. C. P. Members; \$120.00, Non-members. Basic principles of electrocardiography; interpretation based on current knowledge of the physiology of heart muscle. Conger Williams, M.D., *Director*. This course has been registered to full capacity.
- No. 6—**DISEASES DUE TO ALLERGIC AND IMMUNE MECHANISMS**; Haddon Hall Hotel, Atlantic City, N. J.; 4 days, April 28-May 1; \$30.00, A. C. P. Members; \$60.00, Non-members. Immunology, pharmacology, physiology, and clinical phases of diseases caused by immune mechanisms. Given at Atlantic City for convenience of physicians having meetings there at the time. Leo H. Crip, M.D., Associate Professor of Medicine, University of Pittsburgh, *Director*.
- No. 7—**CARDIOVASCULAR DISEASE**; Philadelphia Institutions; 1 week, May 2-7; \$30.00, A. C. P. Members; \$60.00, Non-members. Lectures, panel discussions and clinical demonstrations; recent advances in knowledge, diagnosis and treatment; with an all-star faculty. William G. Leaman, Jr., M.D., F.A.C.P., Professor of Medicine, Woman's Medical College of Pennsylvania, *Director*.
- No. 8—**PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE**; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; 1 week, May 9-14; \$30.00, A.C.P. Members; \$60.00, Non-members. Why symptoms occur; how drugs act; why and how clinical physiological tests are used in diagnosis. Julius H. Comroe, Jr., M.D., F.A.C.P., *Director*.
- No. 9—**ENDOCRINOLOGY**; Tufts College Medical School, Boston, Mass.; 1 week, June 13-18; \$30.00, A. C. P. Members; \$60.00, Non-members. Emphasis on fundamental sciences contributing to endocrinology and recent advances in clinical endocrinology. Edwin B. Astwood, M.D., F.A.C.P., *Director*; E. W. Dempsey, Ph.D., and Roy O. Greep, Ph.D., *Associate Directors*.

For detailed information and registration blanks, address The Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

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### DR. PAUL B. MAGNUSON BECOMES A. C. P. GOVERNOR FOR THE VETERANS ADMINISTRATION

Dr. Paul B. Magnuson who has succeeded to the post as Medical Director of the Veterans Administration, by reason of conditions of the Constitution and By-Laws of the American College of Physicians now is the designated Governor of the College



for the Veterans Administration and, in the future, must be the final endorser of all candidates from that Service.

Dr. Arden Freer, Deputy Medical Director of the Veterans Administration, has been the Acting Governor for that Service for many months, since the retirement of General Paul Hawley as the Medical Director.

#### THE AMERICAN COLLEGE OF PHYSICIANS' DIRECTORY PREPUBLICATION ORDERS DUE

Members of the College who wish to secure copies of the 1949 Directory of the College, to be published next fall if at least 2000 prepublication orders are received, should fill out and return their order forms at once to the College Headquarters. The prepublication price of the Directory to members of the College will be \$4.00; the price to non-members, institutions, and others, \$5.00.

Questionnaires to secure current biographical data will be mailed to members when publication of the Directory has been assured.

Orders should not be accompanied by payment at this time. The Directory will be invoiced when ready for distribution.

#### AMERICAN COLLEGE OF PHYSICIANS REGIONAL MEETINGS

*Colorado, New Mexico, Idaho, Montana and Wyoming*, Denver, Colo., March 1, 1949. A joint meeting for College members from the five States was arranged by the College Governors: Ward Darley, M.D., F.A.C.P., Denver, Colo.; Robert O. Brown, M.D., F.A.C.P. (deceased February 1), Santa Fe, N. M.; Samuel M. Poindexter, M.D., F.A.C.P., Boise, Idaho; and Harold W. Gregg, M.D., F.A.C.P., Butte, Mont. The Program Committee, responsible for the scientific program held at the University of Colorado School of Medicine, included Louis S. Faust, M.D., F.A.C.P., Chairman, and William E. Hay, M.D., Frank B. McGlone, M.D., and William A. H. Rettberg, M.D., A.C.P. Associates; all of Denver, Colo. Luncheon was had at the Colorado General Hospital, and a dinner meeting took place at the Cosmopolitan Hotel, not only for College members and their guests, but also for members of the Medical Society of the City and County of Denver and registrants for the Mid-winter Clinics Group. LeRoy H. Sloan, M.D., F.A.C.P., Chicago, Ill., Member of the Board of Regents, was guest speaker of the evening.

The following papers were presented: Indian Health, Mason V. Hargett, M.D., F.A.C.P., Billings, Mont. A Slide Culture Method for Early Detection and Observation of Growth of the Tubercle Bacillus, John W. Berry, M.D., and Hope Lowry, M.D. (Associates), Denver, Colo. Current Status of Streptomycin Research at Fitzsimons General Hospital, John R. Durrance, Major (MC), U. S. Army, Denver, Colo. Patent Ductus Arteriosus Complicated by Severe Pulmonary Arteriosclerosis and Rheumatic Heart Disease, William E. Hay, M.D. (Associate), Denver, Colo. The Place of Cardiac Catheterization in the Diagnosis of Congenital Heart Disease, George J. Maresh, M.D., Denver, Colo. Diaphragmatic Hernia, John A. Layne, M.D., Great Falls, Mont. The Diagnosis of Gastric Tumors, Frank B. McGlone, M.D. (Associate), Denver, Colo. The Clinical Association of Multiple Myeloma and Allied Conditions, LeRoy H. Sloan, M.D., F.A.C.P., Chicago, Ill. Twenty-Two Year Follow-Up of a Case of Mucous Colitis, Franklin G. Ebaugh, M.D., F.A.C.P., and John M. Lyon, M.D., Denver, Colo. The Management of Lower Nephron Nephrosis (Studies from the Hektoen Institute for Medical Research, Cook County Hospital), William S. Hoffman, M.D., Ph.D., F.A.C.P., Chicago, Ill., and Daniel Marshall, Lieutenant (MC), U. S. Army, Denver, Colo. Congenital Cystic Pancreas in the Adult. Presentation of Two Cases, Martin G. Goldner, M.D., F.A.C.P., Fort Logan, Colo.

A Regional Meeting for the *District of Columbia, Maryland, the U. S. Army, U. S. Navy, U. S. Public Health Service, and the Veterans Administration* was held on February 19, 1949, at the headquarters of the Medical Society of the District of Columbia, Washington, D. C. John Minor, M.D., F.A.C.P., President of the Society, presided over the morning scientific session; Wetherbee Fort, M.D., F.A.C.P., Baltimore, Governor for Maryland, over the afternoon scientific session. Wallace M. Yater, M.D., F.A.C.P., Governor for the District of Columbia, was General Chairman for the meeting and was ably assisted by a committee consisting of Surgeons General Raymond W. Bliss, M.D., F.A.C.P., Leonard A. Scheele, M.D., F.A.C.P., and Clifford A. Swanson, M.D., F.A.C.P., Governors for the U. S. Army, U. S. Public Health Service, and U. S. Navy; Paul B. Magnuson, M.D., F.A.C.P., Governor for the Veterans Administration; Dr. Fort; Drs. Louis K. Alpert, F.A.C.P., Harold J. Jeghers, F.A.C.P., Colonel Charles R. Mueller (MC), U. S. Army, F.A.C.P., Captain Lloyd R. Newhouser (MC), U. S. Navy, F.A.C.P., Monroe J. Romansky, F.A.C.P., J. Lawn Thompson, F.A.C.P., and Joseph J. Wallace, F.A.C.P.

Guest speakers at the luncheon included Walter W. Palmer, M.D., F.A.C.P., New York City, A.C.P. President; George Morris Piersol, M.D., M.A.C.P., Philadelphia, Pa., Secretary-General; Maurice C. Pincoffs, M.D., M.A.C.P., Baltimore, Md., Second Vice President, and Editor of the *Annals of Internal Medicine*; William Gerry Morgan, M.D., M.A.C.P., Washington, D. C., former Governor, Secretary-General, and Regent; and Mr. Edward R. Loveland, Executive Secretary, Philadelphia, Pa.

The scientific sessions contained the following presentations: Radiation Sickness, Eugene P. Cronkite, Lt. Comdr. (MC), U. S. Navy, Bethesda, Md. Infectious Complications of Drug Addiction, Hugh H. Hussey, M.D., F.A.C.P., Washington, D.C. Bone Marrow Culture of Tubercle Bacilli, Sol Katz, M.D. (Associate), Washington, D. C. Treatment of Tuberculous Peritonitis with Streptomycin, Thomas McP. Brown, M.D., Washington, D. C. Panel Discussion on Antibiotics: Recent Advances in Penicillin and Streptomycin, Monroe J. Romansky, M.D., F.A.C.P., Washington, D. C.; Pharmacology of Aureomycin, Harry F. Dowling, M.D., F.A.C.P., Washington, D. C.; Clinical Use of Aureomycin, Emanuel B. Schoenbach, M.D. (Associate), Baltimore, Md.; Chloromycetin, Theodore E. Woodward, M.D., Baltimore, Md. Comments on Stellate Ganglion Block for Angiospasm from Cerebrovascular Thrombosis, Edward B. Tuohy, M.D., Washington, D.C. Intrathoracic, Extracardiac Arteriovenous Fistulae, Wallace M. Yater, M.D., F.A.C.P., Washington, D. C. Gynecomastia, L. H. Kyle, M.D., Washington, D.C. Current Histamine Therapy, Lester S. Blumenthal, M. D. (Associate), Washington, D. C. Recent Developments in Q Fever, Robert J. Huebner, M.D., Bethesda, Md. Clinical Value of the Complement Fixation Test for Amebiasis, Thomas A. Haedicke, Major (MC), U. S. Army, Washington, D. C. Panel Discussion on Bronchial Asthma: Pathologic Physiology, John J. Curry, M.D., Washington, D. C.; Allergy, Harry S. Bernton, M.D., F.A.C.P., Washington, D. C.; Psychiatric Aspects, G. N. Raines, M.D., Washington, D. C.; Inhalation Therapy, Paul F. Jaquet, M.D., Washington, D.C.; Surgical Treatment, Brian Blades, M.D., Washington, D. C. Indications and Limitations of Angiocardigraphy, Albert D. Kistin, M.D. (Associate), Washington, D. C.

The *Nebraska* Regional Meeting of the College took place on February 19, 1949, at the Hotel Paxton, Omaha, under the Governorship of Joseph D. McCarthy, M.D., F.A.C.P., Omaha. The meeting consisted of an afternoon scientific session and a dinner meeting at which Dr. McCarthy presided and Dr. Walter L. Palmer, M.D., F.A.C.P., Chicago, Ill., Chairman of the Board of Governors, spoke on "Problems Confronting The American College of Physicians and the American Board of Internal Medicine."

The medical program was as follows: The Moral Theory of Behavior: A Practical Approach to Diagnosis and Treatment in Psychiatry, Frank R. Barta, M.D.

(Associate), Omaha. Inhalant Allergies: Newer Aspects in Treatment, M. H. Brodkey, M.D. (Associate), Omaha. Use of "Tween 80" in Abnormalities of Fat Absorption, Donald J. Bucholz, M.D. (Associate), Omaha. The Treatment of Intractable Peptic Ulcer, Walter L. Palmer, M.D., F.A.C.P., Chicago, Ill. Propylthiouracil in Hyperthyroidism, Arthur L. Smith, Sr., M.D., F.A.C.P., Lincoln. Addison's Disease, Robert A. Youngman, M.D. (Associate), Lincoln. Clinical Application of Radio-isotopes in Medical Therapy, Howard B. Hunt, M.D., Omaha. Bacteriologic Aspects of Chemotherapy, James M. Severens, Ph.D., Omaha.

The *Virginia* Section of the American College of Physicians met at Norfolk, Va., on February 23, 1949, to enjoy a program arranged by Walter P. Adams, M.D., F.A.C.P., Norfolk, Chairman of the Program Committee, and A. Brownley Hodges, M.D., F.A.C.P., Norfolk, President of the Section. A scientific session was held in the afternoon at the Norfolk General Hospital, and was followed by a reception and dinner meeting at the Norfolk Yacht and Country Club. Guest speaker of the evening was William D. Stroud, M.D., F.A.C.P., Philadelphia, Pa., Treasurer of the College.

The following papers were presented: Hepatitis without Jaundice in Infectious Mononucleosis, Bernard I. Lidman, M.D., F.A.C.P., Norfolk. Pre-Senile States, with Case Presentation, Thomas N. Spessard, M.D., F.A.C.P., Norfolk. Treatment of Tuberculous Lymphadenitis with Streptomycin, J. A. C. Gray, Comdr. (MC), U. S. Navy, F.A.C.P., Portsmouth. Pulmonary Tularemia with Two Cases Treated with Streptomycin, George B. Craddock, M.D. (Associate), Lynchburg. Pelvic Tumors with Ascites Alone and with Hydrothorax (Meigs' Syndrome), Kinloch Nelson, M.D. (Associate), and Charles W. Dennison, M.D., Richmond. Hereditary Hemorrhagic Telangiectasia with Profuse Intestinal Bleeding, John Powell Williams, M.D., F.A.C.P., Richmond. Pseudo-Hemophilia with Case Report, Edward D. Levy, M.D., Norfolk. Rupture of Aortic Aneurysm, Arthur Klein, M.D. (Associate), Richmond. Report of a Case of Stokes-Adams Syndrome, Presumably of Syphilitic Etiology, John Franklin, M.D. (Associate), Norfolk. Pericarditis with Effusion, M. Richard Whitehill, M.D., F.A.C.P., Norfolk. An Unusual Case of Poisoning, Ernest G. Scott, M.D., F.A.C.P., Lynchburg. Chloromycetin in the Treatment of Typhoid Fever, Walter B. Martin, M.D., F.A.C.P., Norfolk. Cardiac Discomfort with Gall Bladder Disease, J. Franklin Waddill, M.D., F.A.C.P., Norfolk.

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#### ADDITIONAL LIFE MEMBERS

The American College of Physicians takes pride in announcing that, by their recent subscriptions, the following Fellows have been added to the Roster of Life Members of the College:

Samuel M. Alter, Los Angeles, Calif.  
 Walter Beckh, San Francisco, Calif.  
 William E. Costolow, Los Angeles, Calif.  
 Edward P. Eglee, New York, N. Y.  
 David Fertig, Hartsdale, N. Y.  
 Harold I. Gosline, Butner, N. C.  
 Robert H. Hackler, Jr., Washington, D. C.  
 Charles Edward Hamilton, Lafayette, La.  
 Albert C. Herring, New York, N. Y.  
 Samuel M. Jacobson, Cumberland, Md.  
 C. Harvey Jewett, Canandaigua, N. Y.  
 J. Allen Kennedy, Nashville, Tenn.  
 Richard E. D. Kepner, Honolulu, T. H.  
 Robert J. Kinney, Topeka, Kans.  
 Philip Krainin, New York, N. Y.

S. T. Laufer, Halifax, N. S., Can.  
Noble D. Leonard, San Francisco, Calif.  
Joseph Litwins, New York, N. Y.  
Gilbert H. Marquardt, Chicago, Ill.  
Bernard J. McCloskey, Jacksonville, Fla.  
Hector J. McNeile, New York, N. Y.  
Robert C. Moehlig, Detroit, Mich.  
James C. Naurison, Springfield, Mass.  
Oscar A. Palatucci, New York, N. Y.  
D. Sergeant Pepper, Philadelphia, Pa.  
Manuel de la Pila Iglesias, Ponce, P. R.  
Francis W. Pruitt (MC), USA, Washington, D. C.  
Richard Reeser, Jr., St. Petersburg, Fla.  
Bertram J. Sanger, New York, N. Y.  
A. G. Schnack, Corona, Calif.  
Roy W. Scott, Cleveland, Ohio  
James W. Sours, Peoria, Ill.  
Charles W. Thompson, Pasadena, Calif.  
Otis S. Warr, Memphis, Tenn.  
E. S. Wegner, Lincoln, Nebr.  
Joseph R. Wiseman, Syracuse, N. Y.  
Arthur A. Wohlrabe, Minneapolis, Minn.  
Robert M. Woods, Los Angeles, Calif.

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#### INTERNATIONAL SOCIETY OF INTERNAL MEDICINE

The International Society of Internal Medicine has been accepted as a founding member of the "Conference de Fondation du Conseil Permanent pour la Coordination des Congres Internationaux des Sciences Medicales," and has been invited to take part at a conference in Brussels from April 4 to 9, 1949.

Dr. Albert M. Snell, F.A.C.P., Rochester, Minn, has been active on the American Committee of this society.

## OBITUARIES

## DR. HARVEY OSCAR ROHRBACH

Dr. Harvey Oscar Rohrbach, a man of many intellectual interests, a fine gentleman and a credit to his profession, died December 9, 1948.

He was born in Longswamp, Pa., on June 27, 1870, and received the following degrees: B.E., in 1893, and M.E., in 1895, from Kutztown State Teachers College; M.D., in 1902, from the Loyola University School of Medicine.

Dr. Rohrbach taught in public schools for a number of years. He was a resident at St. Christopher's Hospital for Children, in Philadelphia, and was consulting pediatrician to St. Luke's Hospital, in Bethlehem, and chairman of the Northampton County Child Health Committee and Certified Milk Commission.

A fellow of the American College of Physicians since 1930, Dr. Rohrbach was also a fellow of the American Academy of Pediatrics and a member of the Philadelphia Pediatrics Society, American Medical Association, Lehigh Valley and Northampton County Medical Societies (former president of the latter society), and the Medical Society of the State of Pennsylvania.

Dr. Rohrbach was an ethical physician and a high-minded citizen.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania.

## DR. RAYMOND L. TRAYNOR

Raymond L. Traynor, M.D., F.A.C.P., was born on February 11, 1894, and died at his home in Omaha, Nebr., November 10, 1948, of a malignant hypertension. He received his Bachelor of Arts and Doctor of Medicine degrees from Creighton University. At the time of his death he was Clinical Professor of Medicine at his Alma Mater.

Dr. Traynor was an exponent of the highest ethical standards in medical practice and a forceful, enthusiastic teacher in his chosen field. He stood for only the best in medicine, and his life will always be a model for the many students who came under his tutelage at Creighton University. Throughout his professional career he was a faithful friend and a kindly and tactful physician. Dr. Traynor had been a Fellow of the American College of Physicians since 1932 and was a diplomate of the American Board of Internal Medicine. He was also a fellow of the American Medical Association, and a member of the Nebraska State Medical Association, the Omaha-Douglas Counties Medical Society and the Omaha Mid-West Clinical Society.

His many friends, his students and the medical profession have sustained a real loss in the death of this able physician.

## DR. ALF HOFF

Alf Hoff, M.D., F.A.C.P., an internist of St. Paul, Minn., and a fellow of the American College of Physicians since 1929, died October 9, 1948.

Dr. Hoff was born in St. Paul, March 9, 1883. After attending the University of Minnesota, where he received his B.S. and M.D. degrees in 1908 and 1910, respectively, he interned in the City and County Hospital, now known as the Ancker Hospital, 1910-11. The following two years he served as assistant to Dr. Ancker. He later became attending physician, chief of a medical service, and subsequently chief of the Division of Internal Medicine of this hospital. Dr. Hoff was also consultant to the Northern Pacific Beneficial Association Hospital, attending physician, Gillette State Hospital for Crippled Children, and chief of staff and a trustee of St. Luke's Hospital. From 1945 he held appointment as clinical associate professor of medicine in the University of Minnesota Medical School.

A diplomate of the American Board of Internal Medicine, Dr. Hoff was a fellow of the American Medical Association, a member of the Minnesota State Medical Association, the Ramsey County Medical Society, the Minnesota Society of Internal Medicine, Minnesota Pathological Society, Minnesota Academy of Medicine, and the American Association for the Advancement of Science.

### CAPTAIN ROY J. LEUTSKER (MC), U. S. NAVY, RETIRED

Roy John Leutscher of Rancho Santa Fe, Calif., Captain in the Medical Corps of the U. S. Navy, Retired, died July 18, 1948, at the age of 57. Dr. Leutscher attended Lawrence College and received his medical degree in 1918 from Northwestern University Medical School. He entered the Medical Corps shortly thereafter and his assignments included tours of duty at the Naval Training Station, San Francisco, with Submarine Division 17, at the Naval Hospitals at Mare Island and San Diego, Calif. From 1928 to 1930, while assigned to the Naval Recruiting Station in Salt Lake City, Dr. Leutscher also held appointments in the Department of Pharmacology of the University of Utah College of Medicine and as Attending Physician in the Salt Lake County General Hospital. He served the Naval Hospital at San Diego as Cardiologist from 1932 until 1937, when he retired from active service. He was recalled to active duty in 1939.

A fellow of the American College of Physicians since 1934, Dr. Leutscher was also a member of the Association of Military Surgeons of the United States, of the Salt Lake County Medical Society, American Medical Association and San Diego Academy of Medicine.

### DR. LOUIS F. RUSCHHAUPT

Dr. Louis F. Ruschhaupt was born in Milwaukee, Wis., on March 10, 1879, and he died on September 30, 1948, of carcinoma of the bladder and diabetes mellitus. He was educated at the University of Wisconsin where he received his B.S. degree in 1899, and at Rush Medical College where he obtained his medical degree in 1902. Following an internship at Johnston Emergency Hospital, Milwaukee, he was Professor of Chemistry at the Wisconsin College of Physicians and Surgeons from 1906 to 1913, and he later served Marquette University School of Medicine as Associate Professor of Medicine from 1919. He had served in the Army Medical Reserve Corps during World War I as a captain, and had taken postgraduate work at Berlin and Vienna. He was a member of the staff of the Milwaukee County, Evangelical Deaconess, Misericordia, and Johnston Emergency Hospitals.

In 1932 Dr. Ruschhaupt became a Fellow of the American College of Physicians and subsequently became a diplomate of the American Board of Internal Medicine. He was a Fellow of the American Medical Association and a member of his local county and state medical societies and of the American Association for the Advancement of Science.

KARVER L. PUESTOW, M.D.,  
Governor for Wisconsin

# ANNALS OF INTERNAL MEDICINE

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## THE EFFECTS OF THE "RICE DIET" UPON THE BLOOD PRESSURE OF HYPERTENSIVE INDIVIDUALS \*

By HENRY A. SCHROEDER, M.D., *St. Louis*, PALMER H. FUTCHER, M.D.,  
*Baltimore, Maryland*, and MELVIN L. GOLDMAN,† M.D.,  
*St. Louis, Missouri*

SINCE Kempner<sup>1</sup> reported alleviation of the elevated blood pressure in cases of arterial hypertension and renal diseases by the use of a diet composed of rice, fruit juices and vitamins, controversy has arisen regarding the manner in which this diet acts. One explanation for its hypotensive effect is that it is poor in salt, as it contains less than 0.5 gm. NaCl per day.<sup>2</sup> Other possible explanations are that the diet is lacking in unknown substances which may play a part in elevating the blood pressure, or less likely, that it contains some material capable of lowering an elevated blood pressure.

In order to evaluate the efficacy of this diet and to study more fully the mechanism by which it affects blood pressure, it was used in seven patients who were in hospital for relatively long periods of time. Modifications of the diet were subsequently made in several cases, in order to determine what substances, if any, when added would counteract its hypotensive effect. The experiences here reported throw light on the degree of change in blood pressure which one can expect in patients treated by this diet. In order to discover any special advantages of this diet, a comparison was made between these changes and those induced by restriction of salt and by hospitalization.

### METHODS

Patients were selected at random from a group being studied in the Out-Patient Department of the Washington University Clinics, the only criteria

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From the Department of Internal Medicine and the Oscar Johnson Institute, Washington University School of Medicine and Barnes Hospital, St. Louis, Missouri.

This study was supported by a grant-in-aid from the U. S. Public Health Service.

The assistance of Miss Dorothy Fraser, R. N., Miss Sallie Wood, R. N., Miss Marlene Hunter, Dietitian, and Miss Julia E. Finn is gratefully acknowledged.

† National Institute of Health Postdoctorate Research Fellow.

being that they suffered from arterial hypertension, that the non-protein nitrogen content of their blood was normal, and that they were willing to remain in hospital for a minimum period of three months. The diet, as prescribed by Kempner (hereinafter called the "rice diet") consisted of three daily feedings, each supplying:

Rice—90 gm. dry weight,  
 Sugar—as desired; 25 gm. average,  
 Fruit juice—200 c.c.,  
 Fruit—2 servings.

The sodium content did not exceed 0.2 gm. Approximately 1750 calories and 24 gm. of protein were supplied daily. Ferrous sulfate, 0.6 gm. and three multivitamin tablets (Upjohn, Unicaps) were administered daily, except in the case of one (A.P.) who was given *Multivits* (White).

Patients spent the whole period of observation in Barnes Hospital, four being allowed out of bed as desired, and three restricted to bed. Blood pressure was measured once or twice a day with the patient in the supine position; the determination in the morning was made before the patient arose and before breakfast, and that in the afternoon after one hour of rest. An

TABLE I  
 Effect of Diet Upon Blood Pressure and Body Weight

No.	Patient	Age Years	Control Period			Experimental Period			Change in Blood Pressure mm. Hg		Weight (lbs.)		Total Hos- pital Days
			NaCl in Diet Gm.	Dura- tion Days	B. P.* mm. Hg	Diet or NaCl Content Gm.	Dura- tion Days	B. P.* mm. Hg	Sys- tolic	Dias- tolic	Initial	Change	
1	L. S. ♀	42	2†	21	191/108	Rice	31**	169/88	-22	-20	182	-10	92
2	S. K. ♀	56	2	13	232/119	Rice	16	224/119	-8	0	104½	-1½	34½
3	A. K. ♂	43	5-8	26	204/119	Rice	21	197/113	-7	-6	154	-1	90
4	L. M. ♂	36	5-8	51	198/134	Rice	25	177/128	-21	-6	129½	-10½	102
5	C. O. ♀	38	5-8	34	156/107	Rice	21	126/93	-30	-14	125	-10	120
6	A. F. ♂	39	5-8	32	168/112	Rice	35	137/93	-31	-19	129	-8	103
7	A. P. ♂	42	1	31	251/163	Rice	90	226/162	-25	-1	117	-13½	121
8	L. C. ♀***	33	8	23	199/123	1	21	167/106	-32	-17	233½	-13	—
9	W. D. ♂	43	8	10	190/119	1	24	164/109	-26	-10	226½	-12	98
10	F. W. ♀†	23	5-8	28	195/132	1	31	163/109	-32	-23	161	-11	90
		23	8	40	183/115	1	50	162/118	-21	+3	144	-7	114
11	I. H. ♀†	40	2	35	148/101	12	23	161/110	+13	+9	187½	-6½	90
8	L. C. ♀***	33	1	21	167/106	8	10	190/119	+23	+13	220½	+6	—
12	D. B. ♀	25	5-8	10	172/111††	5-8	85	143/100††	-29	-11	115	+3½	95
10	F. W. ♀†	23	5-8	14	193/131††	8	40	183/115††	-10	-16	151	-7	—
11	I. H. ♀†	40	2	10	165/115††	2	35	148/101††	-17	-14	192½	-5	—
13	V. R. §	42	8	10	193/126††	8	39	168/113††	-25	-13	130	+5	92

\* Average of all blood pressure readings made during last 7 days of period.

\*\* Pt. received 6 gm. additional NaCl daily for 15 days from 32nd to 46th day. Total duration rice diet 65 days (see figure 1).

‡ Died.

†† Average of first 10 and last 10 days of period of observation.

\*\*\* 1000 calorie diet throughout hospital stay.

† 1200 calorie diet.

§ Case not reported in detail. Renal function was normal and ocular fundi showed only arteriolar narrowing.



observation period of 13 days to seven weeks in hospital served as control during which a normal diet (restricted as to salt or caloric content in three cases) was given. The intake of fluids was not limited. The rice diet was then given for 16 to 90 days (table 1), and a normal diet finally substituted. In two cases an attempt was made to evaluate the effect of adding sodium chloride to the rice diet. All patients except A. K. received a barbiturate sedative each evening throughout the greater part of their hospital stay. The effect upon the blood pressure of three doses of 0.18 gm. of sodium amytal administered at hourly intervals ("sodium amytal test") was measured in four patients during the control period.

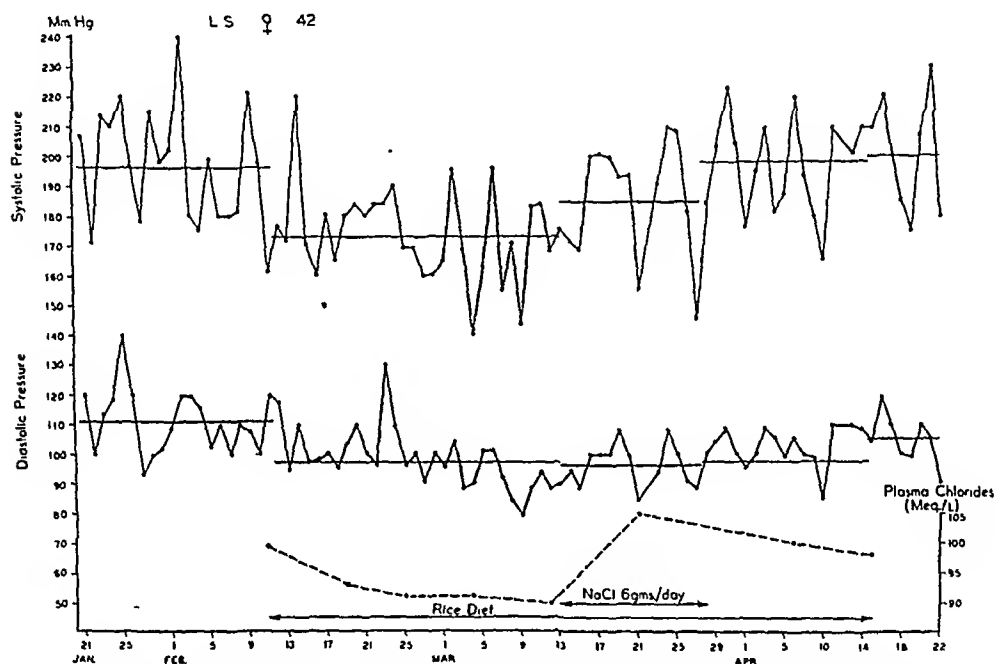


FIG. 1. Case 1, L. S. The straight lines indicate average of all blood pressure measurements recorded during the indicated period of observation. The control period lasted 21 days with the patient on bed rest. From February 11 through March 8 she was allowed up one hour twice daily, thereafter she was up as desired. "Rice Diet" indicates the unmodified diet as described in the text. Before the "Rice Diet," patient was taking a diet containing 2 gm. sodium chloride and 1200 calories. After it, she was given a high protein diet restricted to 1000 calories. Six gm. of salt per day were added to the rice diet from March 13 to 28.

## RESULTS

*Method of Analysis:* The average systolic and diastolic pressure, shown in figures 1 to 9, was calculated from all recorded blood pressures measured during the whole of each period. In order to demonstrate greater changes, if present, however, the average blood pressures for the last seven to 10 days of each period were calculated and shown in table 1. This shorter period, while reflecting changes occurring slowly, may be less accurate an indication of the actual state of affairs.

*Effect of Rice Diet on Blood Pressure after Control Period:* Four of seven patients, A. K., L. M., A. P. and S. K., exhibited a fall in average diastolic blood pressure of less than 6 mm. Hg calculated from readings made during the last week of each period. Of these, S. K. took a normal diet restricted to 2 gm. of salt during the control period, and A. P. one restricted to 1 gm. (table 1). The blood pressures of these four patients were in a relatively

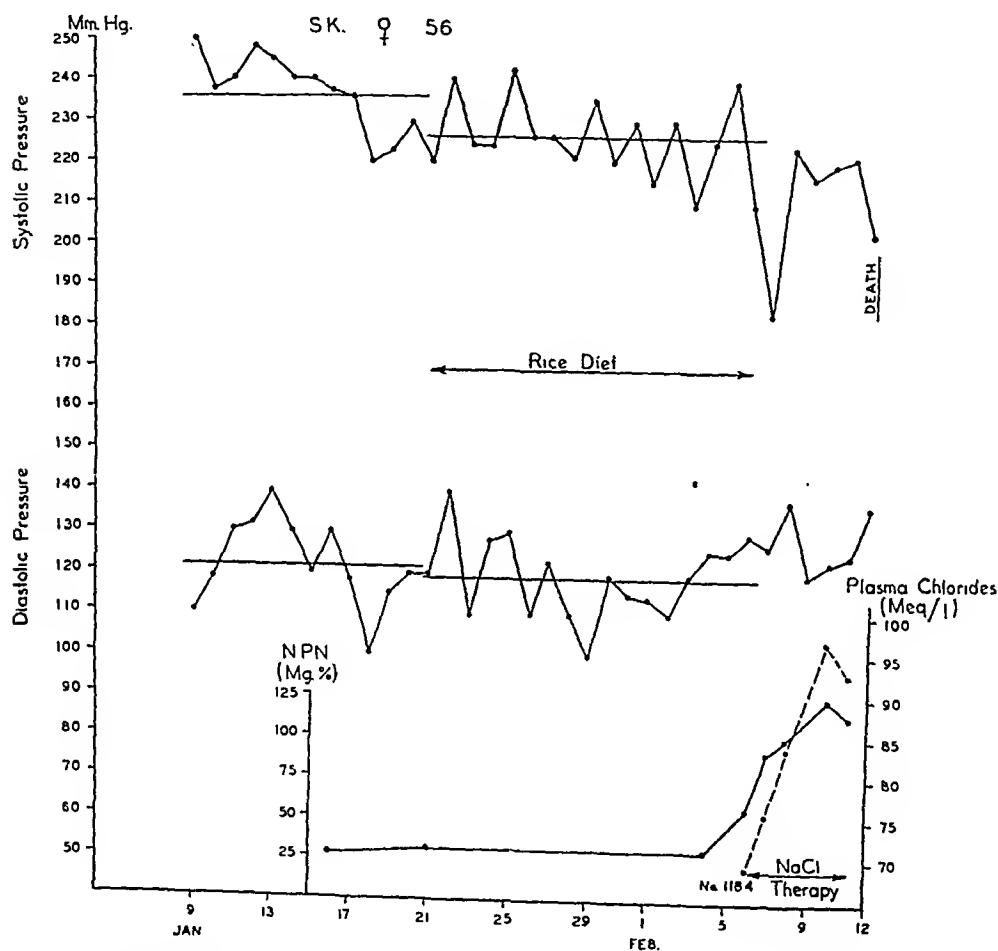


FIG. 2. Case 2, S. K. N.P.N. indicates non-protein nitrogen in the blood. Other notations same as figure 1. Patient remained in bed during study. Control period lasted 13 days. Before the "Rice Diet," the patient was given a normal diet containing only 2 gm. sodium chloride. At NaCl therapy, 33 gm. of sodium chloride were given intravenously in hypertonic solution. Note the absence of significant change in diastolic pressure in spite of a plasma sodium level of 118.4 mEq/l. (See case report.)

high range during the control period, and the change produced by the rice diet was insignificant (figures 2, 3, and 6)\* since the maximum diastolic fall was 6 mm. Hg. Fresh retinal hemorrhages appeared in A. K. after he had been on the rice diet for several days.

Of the remaining three patients, two, A. F., and C. O., subsisted on a normal diet unrestricted as to salt during the control period, and one, L. S.,

\* As insignificant changes in blood pressure occurred in A. K., his chart is omitted.

was given 1200 calories restricted to 2 gm. of salt. Their blood pressures were less elevated during the control period than the others and fell to a level slightly above normal during treatment with the rice diet (figures 1, 4, and 5).

*Effect of Adding Sodium Chloride to the Rice Diet:* For a period of 15 days, 6 gm. of salt were added to the rice diet ingested by two patients, L. S. and A. F. The blood pressure of A. F. was uninfluenced; that of L. S. rose slightly and continued to rise during a subsequent period of 18 days on the rice diet during which no extra salt was administered. In these two patients, therefore, the addition of salt to the rice diet produced no consistent effects during the period of observation (figures 1 and 5).

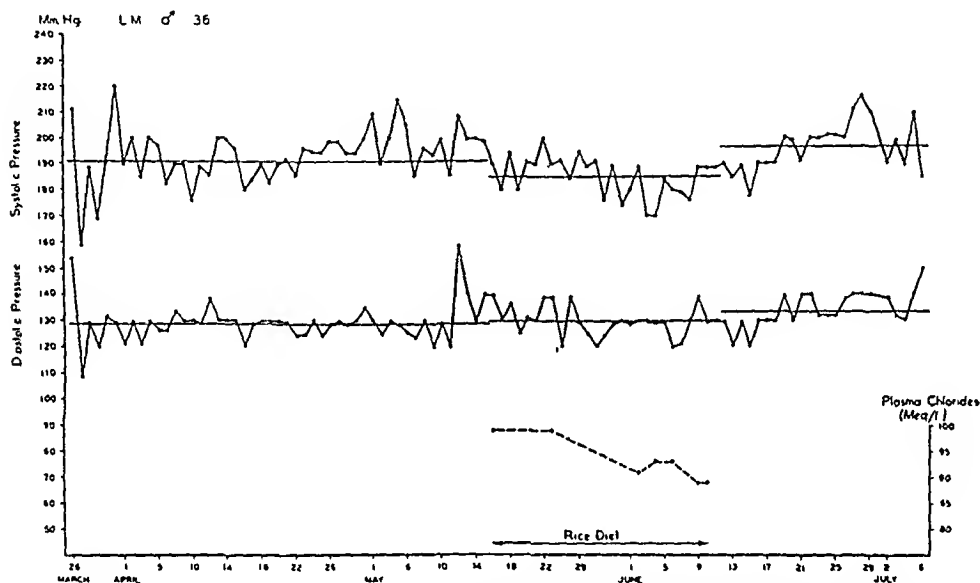


FIG. 3. Case 4, L. M. Patient was ambulatory. Before the "Rice Diet" patient was given a normal diet. After it, he was on a high protein diet. The control period lasted 51 days. Notations same as figure 1.

*Effect of Adding Meat to the Rice Diet:* The addition of 100 gm. of unsalted ground beef to the rice diet ingested by C. O. produced no changes in the diastolic blood pressure during an 11 day period of observation. The systolic blood pressure appeared to rise somewhat (figure 4).

*Effect of Substituting a Normal Diet for the Rice Diet:* Three patients were studied after a normal diet was substituted for the rice diet. After the rice diet was discontinued, C. O. was fed for 50 days a normal diet in which the intake of salt was restricted to 2 gm. In addition, she was given 6 gm. of sodium chloride daily. During this period the blood pressure rose moderately, reaching an average level approximately 20 mm. Hg systolic and 20 mm. diastolic higher than that observed on the rice diet (figure 4).

A. F., after a period of 16 days on the rice diet supplemented by salt, was placed on a high-protein diet unlimited as to salt content, with an additional

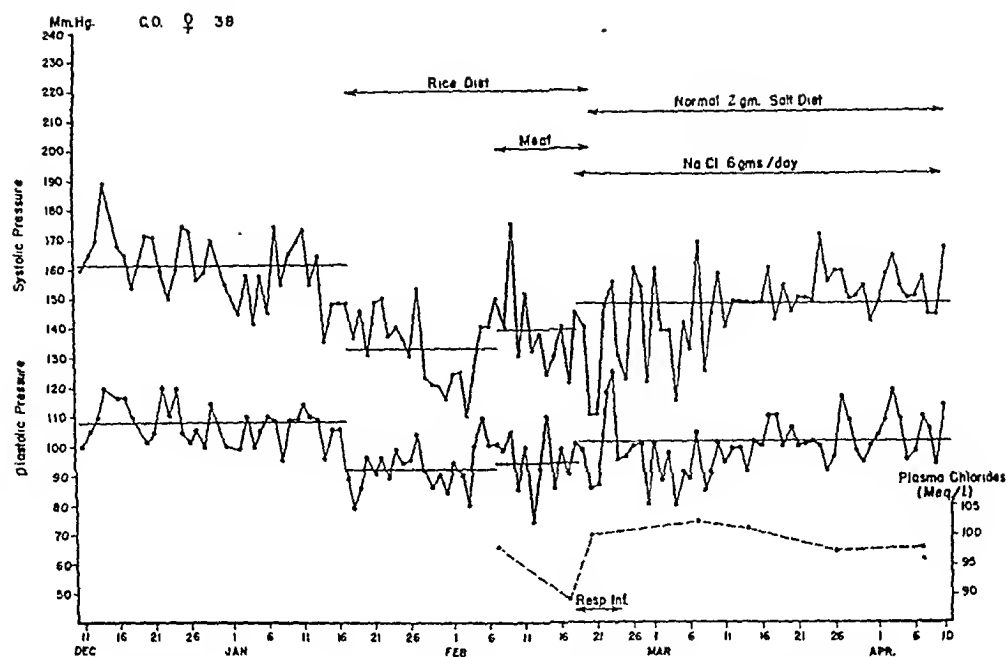


FIG. 4. Case 5, C. O. The control period lasted 34 days. Before the "Rice Diet" patient was on a normal diet. At "Meat" 100 gm. of unsalted ground beef steak was added to the rice diet. Subsequently, she was placed on a normal diet restricted to 2 gm. sodium chloride daily. Note that the level of her blood pressure was almost normal the day the rice diet was started. Notations same as figure 1.

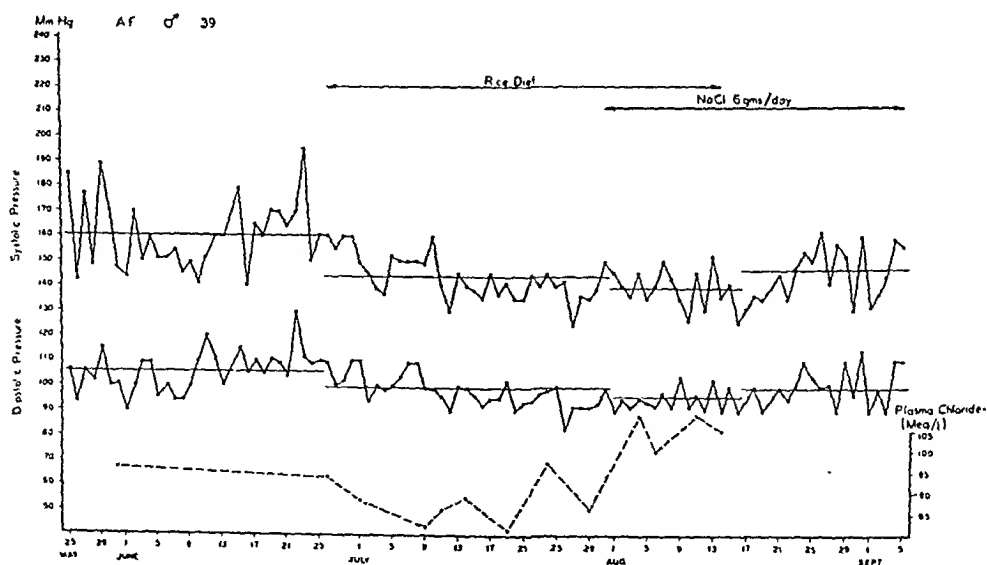


FIG. 5. Case 6, A. F. Patient was ambulatory. The control period lasted 32 days. On July 31, the serum volume, using the dye T-1824, was 2100 c.c.; hematocrit 39 per cent; blood volume 62.35 c.c. per kg. On August 9, serum volume was 2740 c.c.; hematocrit 39.4 per cent; blood volume 4521 c.c.; blood volume 82.6 c.c. per kg. Before the "Rice Diet," patient was on a normal diet. After it, he was given a high protein diet. From July 31 on 6 gm. salt daily were given in addition to the diet. Notations same as figure 1.

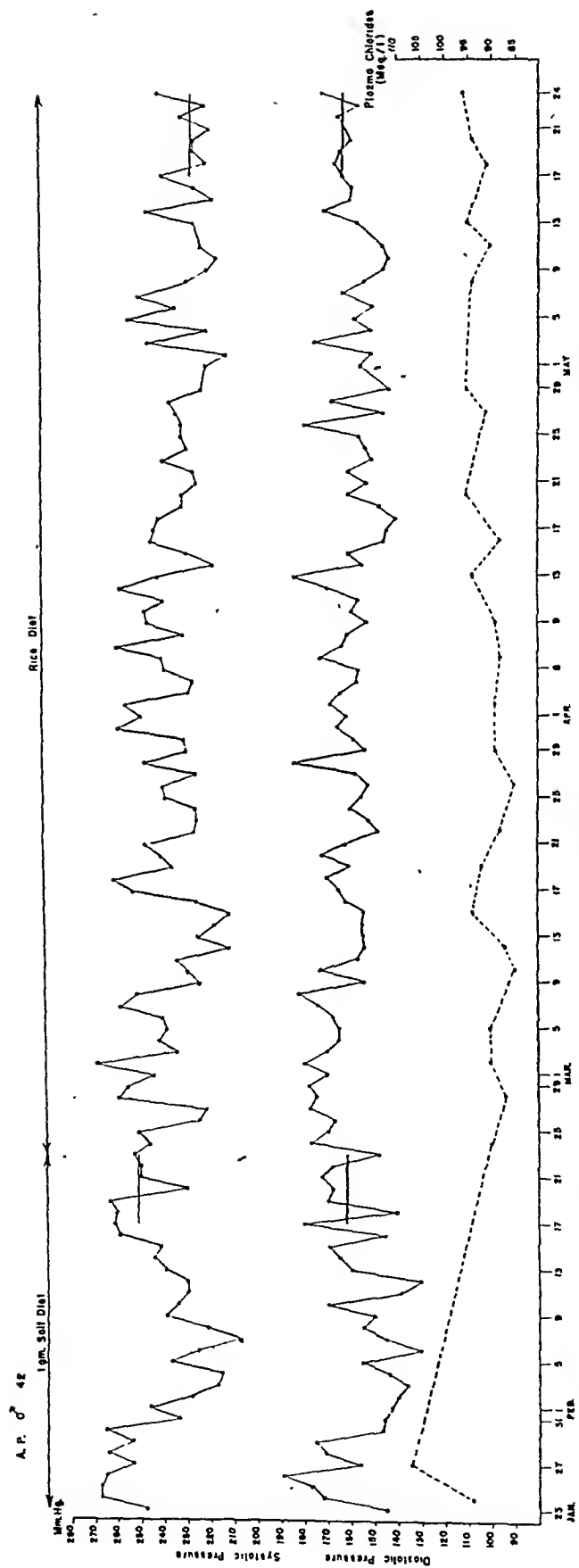


FIG. 6. Case 7, A. P. (Notations same as figure 1.) The control period lasted 31 days. During this period the non-protein nitrogen in his blood had risen from 26 mg. per cent on January 24, to 91 mg. per cent on January 28, and it had decreased slowly to normal levels by the time the rice diet was instituted. The clearance of urea was 33 per cent of normal before the rice diet was started, and 15 per cent of normal at the end without there being nitrogen retention.

6 gm. of sodium chloride daily. The average blood pressure, during 20 days on this regime, exceeded by less than 10 mm. Hg that of the last week of the unmodified rice diet (figure 5).

L. M., after the rice diet, was placed on a high protein diet unlimited as to salt content for 26 days. During this period his average blood pressure was higher by 19 mm. Hg systolic and 5 mm. diastolic than that observed during the last week of the rice diet (figure 3).

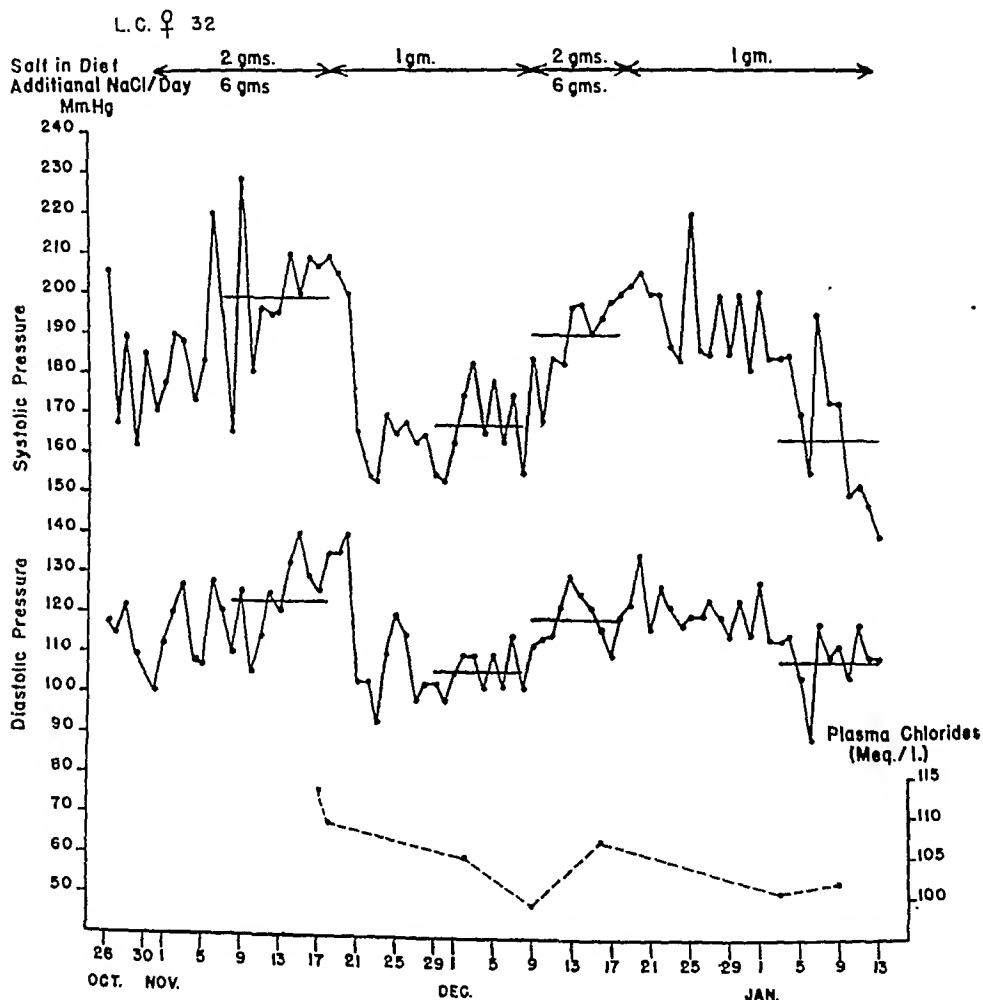


FIG. 7. Case 8, L. C. (Notations same as figure 1.) Throughout the period of observation, calories were restricted to 1000 per day. The control period lasted 23 days. For the first five days the patient was taking a diet unrestricted as to salt. She was ambulatory. Blood pressure levels were influenced by the intake of salt.

Therefore, in one of three patients the replacement of the strict rice diet by normal foods containing average, or higher than average, amounts of salt was associated with a moderate elevation of diastolic pressure above the levels observed while on the strict diet.

*Observations on Plasma Chloride Concentrations:* The administration of the rice diet was associated with a fall in plasma chloride concentration to a

range of 85 to 90 mEq. per liter in six cases and to 69 mEq. per liter in one (figures 1 to 6). There was no obvious correlation between changes in blood pressure and the plasma chloride concentration.

The rice diet did not significantly influence the serum sodium level in three patients with essentially normal renal function (table 2). Ingestion of this diet was associated with an unexplained increase in the normal discrepancy between the concentration of sodium and the sum of the concentrations of chloride and of carbon dioxide expressed as combining power.

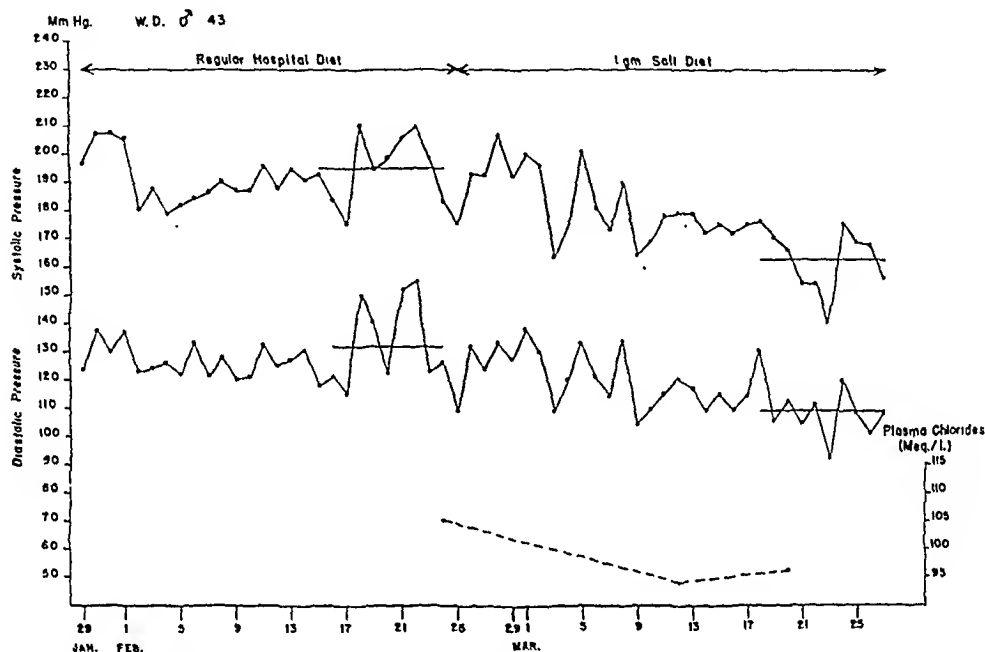


FIG. 8. Case 9, W. D. (Notations same as figure 1.) The control period lasted 28 days. Patient ambulatory. A normal diet was given before salt restriction was instituted. Note that blood pressure did not appear to be influenced until about three weeks after salt restriction was begun.

*Effect of Rice Diet upon Patient with Impaired Renal Function:* The renal function of S. K. was impaired at the start of the period of observation, but the non-protein nitrogen content of the blood was not elevated (figure 2). This patient's subsequent course is presented in detail in the protocol and the graphic chart. After she had ingested the rice diet for 16 days, the chloride content of her serum was found to be 69 mEq. per liter. Concomitantly, she developed oliguria and uremia, and she died a few days later. It seems likely that the rice diet precipitated the episode of uremia because of the restriction of salt which it imposed.

*Miscellaneous Responses to Rice Diet:* The patients found the diet very monotonous; some required considerable encouragement from the hospital staff before agreeing to complete the prescribed period of observation. Several complained of weakness, and five lost considerable weight. The diet did not influence significantly the normal concentrations of serum cal-

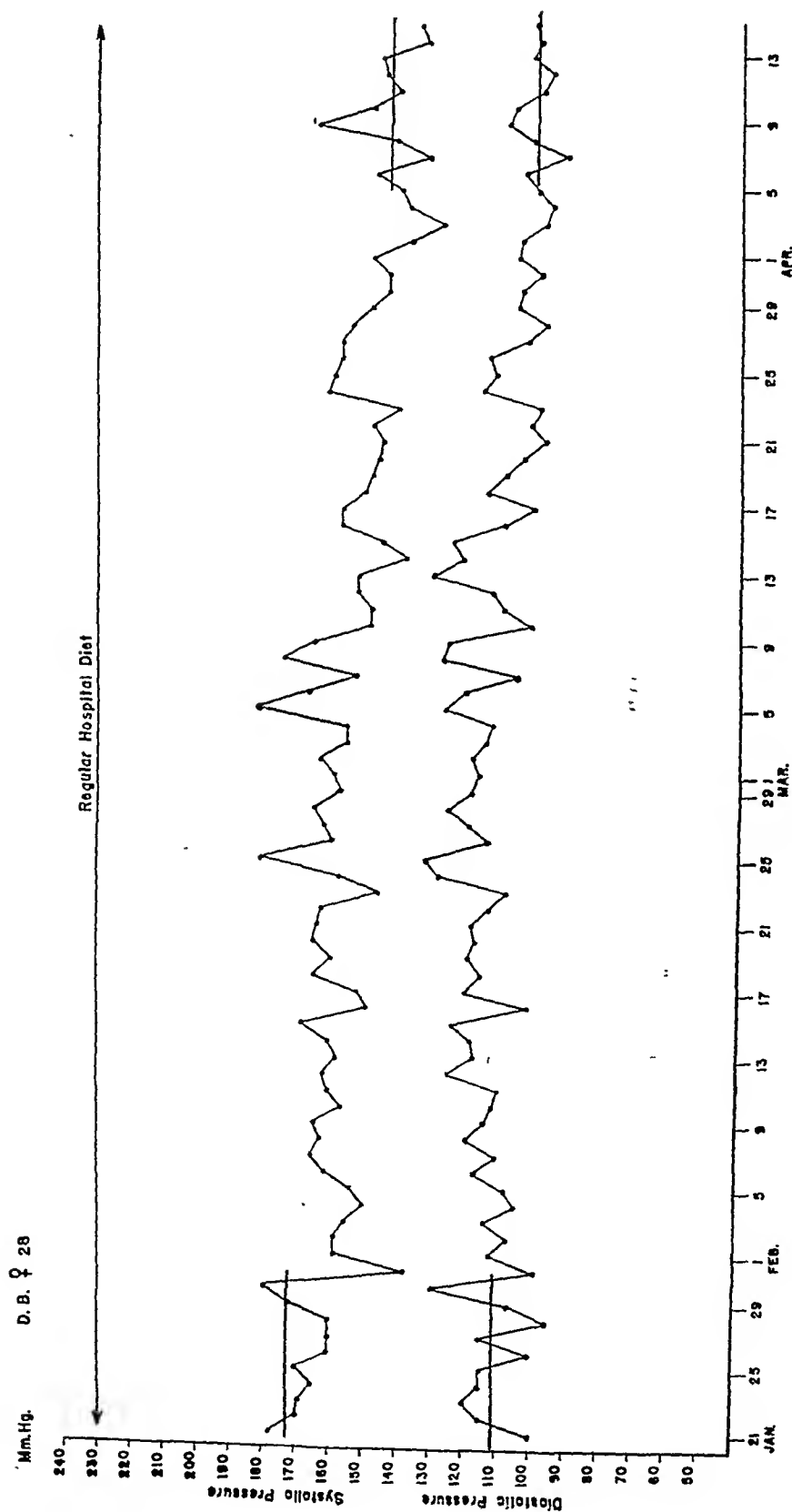


FIG. 9. Case 12, D. B. (Notations same as figure 1.) Patient was given a regular hospital diet throughout her stay. On April 1 a mild upper respiratory infection occurred lasting two days. There appeared to be a gradual decline in the level of blood pressure starting about March 15, that is after almost eight weeks in the hospital.



cium or serum phosphorus of three patients, A. K., L. M., and A. F., in whom measurements were made. The plasma proteins of one became lower; in a second, the values were divergent, but it is possible that they became lower. In four there were no significant changes (table 2).

*The Effect of Moderate Salt Restriction on Levels of Blood Pressure:* In an attempt to compare the results obtained on the rice diet with those expected from restriction of sodium chloride alone, three other patients were

TABLE II  
Blood Proteins and Electrolytes as Influenced by the Rice Diet

Patient	Date	Total Gm. per 100 c.c.	Plasma Proteins Albumin Gm. per 100 c.c.	Globulin Gm. per 100 c.c.	Plasma Chloride mEq. per Liter	Plasma CO <sub>2</sub> Combining Power mEq. per Liter	Serum Sodium mEq. per Liter
L. S.	Feb. 12*	7.2	4.1	3.1	100		
	Apr. 15†	5.5	3.3	2.2	98		
S. K.	Jan. 21*	6.4	3.8	2.6			
	Feb. 6†				69	24.1	118.4
	Feb. 7				76	25.5	
A. K.	Apr. 25*	6.9	4.9	2.0	98	27.0	
	Apr. 28				88	33.6	141.0
	May 16†	7.0	4.8	2.2	85	29.3	140.4
L. M.	May 16*	5.4	3.7	1.7	99	27.7	142.6
	June 10†	5.5	3.7	1.8	89	32.5	144.3
C. O.	Jan. 21*	6.3	4.3	2.0			
	Feb. 17				92	28.1	
	Feb. 18§	6.3	4.3	2.0			
A. F.	May 31	5.7	3.5	2.2	96	31.1	
	June 26*	7.5	4.6	2.9	94	29.4	143.8
	July 29†	5.4	3.1	2.5	86	31.4	142.8
	Aug. 14‡	5.9	3.9	2.0	105	31.4	144.0
A. P.	Feb. 23*	—	—	—	90	30.5	—
	Mar. 28	7.1	4.7	2.4	89	35.0	—
	Apr. 30	7.4	4.6	2.8	95	—	—
	May 24†	7.7	4.9	2.8	96	30.6	—

\* At institution of unmodified rice diet.

† At conclusion of unmodified rice diet.

§ At conclusion of rice diet plus 100 gm. meat.

‡ At conclusion of rice diet plus 6 gm. sodium chloride.

studied under the same conditions (L. C., W. D. and F. W.). In one case, L. C. (figure 7), the average blood pressure fell significantly three days after restriction of salt from a daily intake of 8 gm. to one of 1 gm. This change was reversed after the salt intake was increased to 8 gm. and recurred again but at a slower rate, when the intake was reduced for the second time (table 1). In another, W. D. (figure 8), a significant fall in diastolic pressure occurred after prolonged salt restriction, and in a third, F. W., only the systolic level was affected. Weight was lost by all three, two being re-

stricted also as to calories. These changes were comparable to those seen on the rice diet. Four other patients (not included in table 1) were studied in a similar manner. The effect of salt restriction could not properly be evaluated because other influences may have entered the experiments. No effect of salt restriction was evident.

*The Effect of Adding Salt to a Diet Previously Restricted:* In one case, I. H., blood pressure had fallen slowly to near normal levels on a regular diet containing 2 gm. of salt. When 12 gm. additional salt in enteric coated capsules were given, her blood pressure rose moderately only to fall again when salt was restricted.

*The Effect of Rest plus Salt Restriction:* One patient, M. P., not reported in detail because she was inadequately studied, was put on a normal diet containing 1 gm. of salt on admission to the hospital. She was a 43 year old colored woman with relatively severe hypertension. Her average blood pressure for the first four days of her hospital stay was 220 mm. Hg systolic and 131 diastolic. During the last four days of her 15 day stay it had fallen to 140 and 95 mm. Hg, a change of 60 mm. Hg in the systolic level and 36 in the diastolic. The level of her blood pressure during one year's observation in the Out-Patient Department had been relatively "fixed" at the same or higher values as on admission, and she had suffered from severe headaches and symptoms referable to her heart. Such changes have been seen occasionally on the general medical service.

*Effect of Hospitalization:* One patient, J. O., also not reported in detail, was admitted for study of dietary influences on her blood pressure, which had for several months been approximately 175 mm. Hg systolic and 110 diastolic. She was a 43 year old, white woman who complained of nervousness, headaches, and cardiac pain. On admission her blood pressure was at the level stated, but after 20 days in bed on a normal diet, it averaged 120 mm. Hg systolic and 80 diastolic, a fall of 55 mm. and 30 mm. Hg. The dietary factor could, therefore, not be studied.

Three patients, D. B. (figure 9), F. W. and V. R., were studied in order to evaluate the effect of hospitalization on the levels of blood pressure (table 1). Diastolic pressures fell an average of 11, 16, and 13 mm. Hg after being in hospital 85, 40, and 39 days respectively. In one, the diet was restricted as to calories. These cases are mentioned only for the purpose of bringing attention to the importance of the control period and of other influences which may affect the levels of blood pressure.

## DISCUSSION

This study differs from that of others<sup>1,3</sup> in that the control period of observation in hospital was usually considerably longer in our study (21 to 51 days). Therefore, changes in blood pressure associated with hospitalization and rest could be discounted. These changes may be great. Several additional patients selected for this regime who appeared, from previous

observations, to be suffering from moderately severe hypertension, were not studied because their blood pressures fell to normal levels in the hospital.

Although the average blood pressure levels of three of seven patients declined when they took the strict rice diet, the changes observed were not striking. While it is possible that these moderate changes were occasioned by some specific effect of this dietary regime, it is also possible that continued rest in hospital, the encouragement occasioned by a new form of therapy, or some relatively non-specific metabolic disturbance accompanying the weight loss gave rise to these results.

The blood pressure of the other four patients showed little or no response to the diet. In fact, the general condition of two of the four deteriorated. Additional hemorrhages appeared in the retinas of one, A. K., and the other, S. K., developed hypochloremia and fatal uremia. These four exhibited higher blood pressures than did the three who showed changes on the diet. Hence, they belonged to just that group for which some effective form of therapy is desirable. It is possible that the responses to the rice diet of one of the patients in each group (S. K. and L. S.) were modified by limitation of their daily intake of salt to 2 gm. during the preceding control period.

Ingestion of additional sodium chloride by two patients on the rice diet produced no consistent effect. Substitution of a normal diet for the strict rice regime caused possibly significant elevations in the diastolic pressure of only one of three patients. The inconsistencies of response observed in these few experiments prevent the drawing of definite conclusions concerning the mechanism by which the rice diet produces the beneficial effects reported by Kempner.<sup>1</sup>

There is no doubt that the use of diets restricted as to salt will lower the blood pressure of *some* hypertensive patients. The use of these regimes only rarely achieved a maximum fall of 40 mm. Hg systolic and 30 mm. Hg diastolic,<sup>2, 4, 5</sup> although better results have been reported on out-patients.<sup>6</sup> From the past experience of one of us (H. A. S.), a rough estimate can be made that the blood pressure of only about 10 per cent of an unselected group of patients with well-established hypertension will fall to normal under the influence of a diet restricted only as to salt.<sup>8</sup> Grollman and his co-workers<sup>2</sup> have also pointed this out. It is difficult to predict whether a given patient with hypertension will respond favorably to restriction of salt.

In the cases here reported, restriction of salt alone to amounts twice that in the rice diet produced changes in blood pressure in two patients which were similar to those produced by rice. In two others salt restriction or addition appeared to have a definite, although minimal effect, also comparable to those seen after use of the rice diet. Hospitalization alone caused a definite effect in three, and this added to salt restriction was effective in two others. Restriction of calories plus hospitalization affected one favorably. It should be emphasized, however, that these changes, as in the case of the rice diet, were seen, with two exceptions (W. D. and L. C.), in those patients with less severe forms of the disease. When the condition is well advanced

and necessitates some form of therapy, neither salt restriction nor the rice diet seems to be efficacious.

On the basis of this experience, it must be concluded that the rice diet is of questionable value in the treatment of most cases of hypertension, since in none of seven did striking benefits occur; indeed, the diet appeared to be harmful to one patient. It must be pointed out, however, that in only one of our seven cases (A. P.) was the diet continued for as long a period of time as was recently advocated by Kempner,<sup>7</sup> although the charts published in his earlier reports<sup>1</sup> suggested that the response might occur fairly soon after the diet was begun. It should also be noted that the *regime* used in this study was similar to that of Kempner only as concerns dietary aspects; psychotherapeutic influences were excluded insofar as possible (patients agreeing to take the diet as an experiment with no assurance of benefit to themselves), the control period was long, and four had been restricted as to salt previously. The patients were not informed as to their progress or level of blood pressure until the conclusion of the experiments. The patients used in this study were perhaps younger than many of those indicated by Kempner in his reports.<sup>1, 7</sup>

It appears to us that the *regime* advocated by Kempner<sup>7</sup> has at least four and possibly more factors which need evaluation: The diet is very low in protein and fat, it is very low in salt, and it has strong psychotherapeutic influences. Furthermore, control periods in hospital which we consider adequate have not been shown in his publications. Our study has attempted to evaluate only the *rice diet* itself as an influence on the level of blood pressure. Because of other factors, such as psychotherapeutic influences, the rice diet regime may well be more efficacious than the diet alone. Until advantages of this diet, which have escaped our attention, have been demonstrated, it would appear that diets merely low in salt, protein, or calories are preferable to the as yet unjustified rigors of the rice diet for use by those attempting to treat hypertension by dietary means alone.

#### SUMMARY AND CONCLUSIONS

1. Seven patients suffering from arterial hypertension of varying degrees of severity were treated by a diet containing unsalted rice, fruit juices and vitamins, after adequate control observations were made.

2. Diastolic blood pressures were somewhat lower in three while on the diet, but the changes were not striking. Pressures were essentially unchanged in the other four. One patient with impaired renal function developed marked hypochloremia with uremia and died.

3. The addition of sodium chloride in two cases and the substitution of a normal diet in three did not consistently reverse the effects of the rice diet.

4. Changes in blood pressure occurring in other patients after restriction of sodium chloride alone were of similar magnitude to those observed with

the use of the rice diet. Similar changes have occasionally occurred following hospitalization alone, without alterations in diet.

5. On the basis of this study, a diet of unsalted rice, fruit juices, and vitamins is of questionable value in the treatment of most patients with arterial hypertension. When the disease process was advanced, neither salt restriction nor the rice diet appeared to be efficacious.

#### CASE REPORTS

*Case 1.* L. S., a 42 year old, white, married woman, entered Barnes Hospital complaining of weakness and thoracic pain of 24 hours' duration. The onset of her hypertension occurred at the age of 29 during her second pregnancy. Hospitalization was required because of an elevated blood pressure, labor being induced in the eighth month. About a year later sugar was found in her urine, and she was placed on a low carbohydrate diet and given 20 units of insulin a day, which she continued to take for two years. Her blood pressure remained elevated continuously and was unaffected by a low-salt diet and by sedatives. In 1944, it was at a level of 200 mm. Hg systolic and 124 diastolic. Late that year, she noticed dyspnea and slight ankle edema, but this was not a troublesome complaint until August 1946, when she became confined to bed with dyspnea, orthopnea, edema, and headaches. Her urine was said then to be infected. Precordial pain appeared with radiation down the left arm, and her blood pressure was recorded as high as 270 mm. Hg systolic. She first entered Barnes Hospital because of cardiac pain in August 1946. On physical examination she was moderately obese. Her heart was enlarged, and her blood pressure was 245 mm. Hg systolic and 125 diastolic. The urine contained traces of albumin intermittently, but renal function was within normal limits. A low-salt diet did not affect her blood pressure, but she was discharged with instructions to continue taking it. Headaches and precordial pain continued, and she was readmitted on January 20, 1947, for the latter complaint. Other facts in her history were non-contributory.

On examination, the patient was markedly obese and moderately orthopneic. The arterioles in her ocular fundi were spastic and narrowed, and the veins were nicked. There were small pin-point and flame-shaped hemorrhages in both eye-grounds. The heart was moderately enlarged to the left but was otherwise not remarkable. There was pitting edema of the ankles. Blood pressure was 236 mm. Hg systolic and 124 mm. Hg diastolic.

Retrograde pyelograms were interpreted as showing either moderate bilateral hydronephrosis or large extrarenal pelves. The non-protein nitrogen of the blood was 14 mg. per 100 c.c., and renal function, as judged by the excretion of phenol-sulfonephthalein, was within normal limits. Urea clearance was 95 per cent of normal. The urine was sterile on culture. No evidence of a coronary occlusion was found.

Summary: A 42 year old woman suffered from severe arterial hypertension which was probably entering the malignant stage. Figure 1 shows the course of her blood pressure and other measurements during the ingestion of the rice diet, which was begun 21 days after admission.

*Case 2.* S. K. was a 56 year old, white widow who had suffered from arterial hypertension for at least nine years. She was first admitted to Barnes Hospital in May 1946, because of slight dyspnea, orthopnea and ankle edema, and because anginal pain, occipital headaches and signs of vascular insufficiency in the legs were noted. A right lumbar sympathectomy was performed, and improvement of the circulation to the homolateral leg resulted. Her blood pressure, which was at a level of 190 mm. Hg systolic and 119 diastolic, was unaffected. Because of increasing weakness, fatigue and orthopnea, without ankle edema, she was readmitted on January 8, 1947,

for study. Examination at this time showed a blood pressure of 260 mm. Hg systolic and 130 diastolic. In both ocular fundi there was tortuosity and spasm of the arterioles with a copper-wire appearance, and extreme nicking of the veins. There were numerous hemorrhages and exudates in both eyegrounds. Slight enlargement of the heart was noted. A systolic murmur was heard in the axilla, and an early diastolic murmur was audible along the left sternal border. There was marked thickening of all peripheral arteries, but there were no other remarkable findings. Her urine was sterile on culture. Blood urea nitrogen was 23 mg. per 100 c.c., and she was unable to concentrate urine to a specific gravity of more than 1.012. She was given the rice diet (figure 2).

Fourteen days later she began to complain of severe shortness of breath and prostration. She gradually lost consciousness and Cheyne-Stokes respirations developed. The white blood cell count rose to 35,400 with 94 per cent polymorphonuclear leukocytes. The rectal temperature rose to 38.6° C. The output of urine diminished markedly, varying between 40 and 270 c.c. per day during the next eight days. Plasma chlorides were found to be 69 mEq. per liter, and the non-protein nitrogen of the blood was 56 mg. per 100 c.c. The CO<sub>2</sub> combining power was 24.1 mEq. per liter, and the serum sodium 118.4 mEq. per liter. Subsequently, the non-protein nitrogen in the blood rose to 100 mg. per 100 c.c., although the plasma chloride concentration was elevated by the intravenous administration of 33 gm. of sodium chloride. In spite of this therapy, she died in coma, with acute uremia apparently the cause of death. Autopsy showed arteriolar nephrosclerosis, with petechiae in the renal cortices; fibrinous peritonitis and pericarditis; hypertrophy and dilatation of the heart; and general arteriosclerosis which was of an advanced degree in the abdominal aorta, coronary arteries and splenic artery.

Summary: This 57 year old woman suffered from severe hypertension in the malignant phase; she exhibited diminution of renal function without nitrogen retention. Her course on the rice diet, which terminated in death, is outlined in figure 2.

Case 3. A. K. was a 43 year old, white male who had suffered from arterial hypertension for at least one year. His only complaint was fatigue. Nine months before admission partial paralysis of his right side occurred, which slowly disappeared in a few weeks. Other than that, he was well and working as a blacksmith. The remainder of his history was non-contributory. He was admitted to Barnes Hospital on March 31, 1947. On physical examination, his systolic blood pressure was 240 mm. Hg and his diastolic 130. Aside from slight enlargement, the heart was not remarkable. In the ocular fundi there was slight papilledema, and the vessels showed some thickening without hemorrhage or exudate. His urine contained a trace of albumin and an occasional cast. The non-protein nitrogen in the blood was 20 mg. per 100 c.c. Urea clearance averaged 72 per cent of normal, and he was able to concentrate urine to a specific gravity of 1.019. Several cultures of the urine revealed *Staphylococcus aureus*. Retrograde pyelograms showed slight blunting of the calyces of the right kidney. The lowest blood pressure recorded during the sodium amytal test was 160 mm. Hg systolic and 90 mm. diastolic.

Summary: This 43 year old man exhibited severe hypertension which was uninfluenced during his hospital stay; he was in the early malignant phase. Renal function was slightly diminished. No effect of the rice diet was seen. While he was taking the diet, fresh hemorrhages and exudate appeared in the ocular fundi.

Case 4. L. M. was a 36 year old, white male who had suffered from arterial hypertension for five years. His blood pressure was discovered to be elevated on routine examination. One year before admission, he began to notice weakness and incoördination of his left hand. Otherwise, his history was not remarkable. On physical examination, his blood pressure was 205 mm. Hg systolic and 135 diastolic. His hands and feet were cold and clammy. In his ocular fundi there was marked tor-

tusosity, narrowing and spasm of arterioles with nicking of the veins. One small area of yellow exudate was seen. Aside from slight enlargement, the heart was not remarkable. There was hyperactivity of the deep reflexes of his left arm, which showed lack of coördination. Hoffman's sign was present. There were disturbances of sensation in this extremity. The non-protein nitrogen in the blood was 15 mg. per 100 c.c. Several cultures of the urine revealed coliform organisms. The urine was not remarkable. Intravenous pyelograms revealed normal appearing renal pelves and ureters. The urea clearance averaged 83 per cent of normal, and he was able to concentrate urine to a specific gravity of 1.026. The lowest blood pressure recorded during the sodium amytal test was 120 mm. Hg systolic and 90 mm. diastolic.

Summary: A 36 year old man had suffered permanent partial paralysis of his hand probably as a result of severe hypertension. The effect of the rice diet upon his blood pressure is seen in figure 3.

Case 5. C. O. was a 38 year old, unmarried white woman complaining of dizziness and headaches for several years. At the age of 17, she first began to have recurrent nosebleeds, and her blood pressure was found to be elevated. The nosebleeds occurred intermittently for the next five years. She also noticed occasional fainting spells, dyspnea, and headaches during the succeeding years. Prior to admission, dizzy spells, associated with headache, became more severe, and she also complained of palpitation. Examination showed a blood pressure varying between 160 and 240 mm. Hg systolic and 100 and 150 mm. diastolic. There was some excess hair in the axillae and over the extremities. Her heart was not remarkable except for a soft systolic murmur heard at the apex. The ocular fundi showed vessels which were narrowed with some nicking of the veins. She was able to concentrate urine to a specific gravity of 1.026; the clearance of urea was 71 per cent of normal. The urine contained traces of albumin; cultures of the urine showed the presence of *Staphylococcus aureus* intermittently. Intravenous pyelograms revealed no renal abnormalities. The lowest blood pressure recorded during the sodium amytal test was 100 mm. Hg systolic and 70 mm. diastolic.

Summary: This 37 year old woman had suffered from fluctuating hypertension for 20 years. There were no signs of marked damage to any organ. Headaches were unrelieved by the rice diet. Figure 4 summarizes her course.

Case 6. A. F. was 39 year old white man whose hypertension was discovered on routine examination in 1943. In 1929, he had passed a small stone *per urethram*, an episode preceded by pain in the right flank and hematuria. Headaches had appeared a year before admission but were not incapacitating. Two months before admission he again noticed hematuria and complained of aching pain in his perineum. Hematuria persisted, and he was admitted for this complaint. His blood pressure had varied from 200 to 160 mm. Hg systolic during the four years prior to entry. On examination, his systolic pressure was 200 mm. Hg and 105 diastolic. In his ocular fundi there was narrowing of the arterioles with some nicking of the veins. His heart was not remarkable, and there were no other gross abnormalities noted. Retrograde pyelograms showed a small calculus in his left renal pelvis as the only abnormality. Aside from an occasional red blood cell, his urine was not remarkable. Cultures of the urine revealed a non-hemolytic streptococcus intermittently, and on one occasion, a few colonies of *Staphylococcus aureus*. He was able to concentrate urine to a specific gravity of 1.022. Urea clearance was 117 per cent of normal. The lowest blood pressure recorded during the sodium amytal test was 118 mm. Hg systolic and 80 mm. diastolic.

Summary: This 39 year old man suffered from moderate hypertension and renal calculus. The effect of the rice diet is shown in figure 5.

Case 7. A. P. was a 42 year old, white man who was admitted to the hospital in a stuporous condition. There was no history of previous hypertension. He had complained of severe headaches for six weeks, and on the day of admission suddenly

lapsed into coma without warning. On examination, he was acutely ill, irrational, and disoriented. In the ocular fundi there were extremely narrowed arteries, with several hemorrhages and areas of exudate. The heart was slightly enlarged but was otherwise not remarkable except for a variable arrhythmia which disappeared shortly after admission. A high-pitched, blowing diastolic murmur was heard localized in the fourth left intercostal space. His systolic pressure on admission was 290 mm. Hg and diastolic 180. Neurological examination showed no signs of a localized lesion. The non-protein nitrogen in his blood was 26 mg. per cent. There was marked albuminuria with a few red blood cells in the centrifuged sediment. During the first week he exhibited low-grade fever. His blood pressure remained at the same levels as on admission. The non-protein nitrogen in his blood became elevated to 91 mg. per cent. The patient slowly recovered from his stuporous condition during the next week or 10 days and the non-protein nitrogen level of his blood gradually returned to normal during a month's time. The urea clearance was 33 per cent of normal. After a month in the hospital, he was asymptomatic although the level of his blood pressure had not changed appreciably, his diastolic varying between 180 and 160 mm. Hg. He was placed on the rice diet for a period of three months without effect on his blood pressure. At the end of this time, the urea clearance was 15 per cent of normal, and there was only a trace of albumin in the urine.

Summary: Fulminating hypertension with renal impairment in a 42 year old man whose first symptom was an attack of encephalopathy. His course on the rice diet, which did not affect the level of his diastolic pressure, is shown in figure 6.

Case 8. L. C. was a 33 year old, unmarried, colored woman who was first found to have arterial hypertension at the age of 27, when she suffered a severe nosebleed. She had no complaints until 14 months before admission when an episode of dyspnea, blurring of vision, dizziness, and ankle edema occurred. Eleven months before this study (November 1946) she had been admitted to this hospital because of a sub-arachnoid hemorrhage, the signs of which cleared slowly. Her blood pressure on a low-salt diet fell from a level of 200 mm. Hg systolic and 130 diastolic to normal levels, the lowest point being 110 mm. Hg systolic and 70 diastolic. Her weight at that time was about 300 pounds. Ever since puberty she had noted an excess of hair on her chin and chest, and it was necessary for her to shave her face about twice a week. Obesity, difficult to control, had been present since then. Although the classical findings of Cushing's syndrome were absent, obesity of the trunk and face and hirsutism were highly suggestive. At the time of admission she had no complaints.

On physical examination, she was markedly obese, with the obesity confined to the trunk, thighs, upper arms, and face. There was a well-developed beard on the chin and a slight mustache. There were pale striae about the arms, back, buttocks, and thighs. There were no hemorrhages or exudates in the ocular fundi, although the arterioles were markedly thickened with irregular areas of constriction. The margins of the optic discs were blurred. Except for a loud, harsh, low-pitched, systolic murmur heard over the precordium and some enlargement, the heart was not remarkable. Laboratory findings were non-contributory; she was able to concentrate urine to a specific gravity of 1.026, and the clearance of urea was 139 per cent of normal. Glucose tolerance test was normal, and no excess 17-ketosteroids were found in her urine, the amount being 3.3 mg. in 24 hours. She excreted 13 mg. of sodium pregnanediol glucuronide in 24 hours.\* The urine was remarkable in that it never contained albumin or abnormal microscopic elements in repeated examinations.

Summary: This 33 year old woman suffered from marked obesity, hirsutism, and severe arterial hypertension for six years. Her blood pressure appeared to respond to variations in the intake of sodium chloride, as seen in figure 7.

Case 9. W. D. was a 42 year old, white, married railroad worker, whose blood pressure was found elevated one year previously. His complaints consisted of fatigue,

\* Determinations made by Dr. W. M. Allen.



mild exertional dyspnea, and one attack of weakness of his right side which gradually improved during several weeks. He also complained of severe occipital headaches and transient numbness in his right hand and arm.

On examination, the ocular fundi revealed marked narrowing of the arterioles without hemorrhage, exudate or papilledema. There was slight cardiac enlargement. Neurological examination showed hyperactive deep reflexes on the right. His clearance of urea was 87 per cent of normal, and he was able to concentrate urine to a specific gravity of 1.021. There was moderate albuminuria without abnormal microscopic elements. The average plasma clearance of para-amino hippurate was 360 c.c. per minute, and of mannitol 96.5. Albuminuria disappeared during his stay in the hospital.

Summary: A 42 year old man with arterial hypertension of at least one year's duration, who showed only slight diminution of renal function. His blood pressure appeared to be lowered by restriction of salt (figure 8).

*Case 10.* F. W. was a 23 year old, white, unmarried woman whose blood pressure was found elevated only three months previously. She had been complaining of headaches and increasing nervousness for five years. On one occasion, six months before admission, she had noticed choking sensations and shortness of breath lasting several hours. This recurred two months later. She had also noticed swelling of her ankles. On examination, she was moderately obese. There was some thickening of the arterioles in the ocular fundi with no hemorrhage or exudate. There was slight enlargement of her heart; otherwise, the examination was not remarkable. There was no albuminuria, although she was able to concentrate urine to a specific gravity of only 1.016. The clearance of urea was 48 per cent of normal. There were no abnormal findings on intravenous urography. It was noted that a typical "diencephalic" blush appeared on embarrassment or emotion, associated with severe spells of crying and emotional outbursts.

Summary: A 23 year old woman suffered from arterial hypertension with diminution of renal function. Her diastolic pressure was not lowered by restriction of salt (table 1).

*Case 11.* I. H. was a 43 year old, white, married woman who had had known hypertension for 11 years which apparently developed in the seventh month of her first pregnancy, associated with toxemia. Two years later another pregnancy was interrupted because of severe hypertension and vomiting. She had no symptoms until three years before admission, when occasional right sided occipital headaches, dizziness, palpitation, fatigue and dyspnea on exertion appeared. Several episodes of dizziness and blurred vision and headache in the interim made her most uncomfortable. She had been obese for many years. She had been followed in the Washington University Clinics where her blood pressure ranged from 198 to 238 mm. Hg systolic and 120 to 140 diastolic. On physical examination, she was very obese with the obesity most marked in the trunk and proximal parts of the extremities. In her ocular fundi were irregularities in caliber of the arterioles without hemorrhage or exudate. Her heart was slightly enlarged but otherwise was not remarkable. There were no other findings of note. In her urine was a moderate amount of albumin with a few red blood cells in the centrifuged sediment. She was able to concentrate urine to a specific gravity of 1.023, and her clearance of urea was only 55 per cent of normal. On admission, she was placed on a diet containing 2 gm. of sodium chloride, following which her blood pressure fell at times to normal levels. When her intake of sodium chloride was raised to 12 gm. per day, her blood pressure became more elevated; later restriction of salt was followed by a fall in her systolic pressure to 130 mm. Hg and her diastolic to 80.

Summary: This 40 year old woman had suffered from arterial hypertension for 11 years, beginning apparently with a toxemia of pregnancy. She was also obese.

The addition of salt to her diet appeared to raise the average level of her blood pressure slightly, and a subsequent withdrawal seemed to lower it (table 1).

*Case 12.* D. B. was a 28 year old, white, married woman complaining of fatigue, fullness in her head, and flushing of the face, hands and arms. Her first admission was in 1944 because of hypertension, discovered at the age of 23. Her blood pressure then was 172 mm. Hg systolic and 118 diastolic, and there were no signs of damage to any organ or system. Her blood pressure was noted to be quite labile during her stay. She was readmitted in 1946 when albuminuria was first noted. At that time, there had been a decline in the ability of her kidneys to concentrate urine to more than a specific gravity of 1.023, and her clearance of urea was 66 per cent of normal. A lumbar sympathectomy was performed which only temporarily influenced the level of her blood pressure. Her third admission was in June 1947 for unexplained fever. At that time, there were few changes in her renal function and none in the level of her blood pressure which remained elevated. She was readmitted in February 1948 for study. On examination, there were no remarkable findings. The ocular fundi showed arterioles only slightly thickened. During the examination, a blotchy erythema appeared over the arms, face and chest which was typical of the "diencephalic" blush. There was no albuminuria, and she was able to concentrate urine to a specific gravity of only 1.020. The clearance of urea was 104 per cent of normal. Glucose tolerance test was not abnormal. Her renal plasma flow, using para-amino hippurate, was 485 c.c. per minute and mannitol clearance was 109. These figures were essentially normal for her size. Her blood pressure was quite labile, and the "diencephalic" blush appeared at frequent intervals during examinations.

*Summary:* This 28 year old woman suffered from arterial hypertension of the "neurogenic" type for five years without damage to any system. Lumbar sympathectomy had not influenced the level of her blood pressure, which did, however, fall somewhat after three months' hospitalization (figure 9).

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# RHEUMATOID SPONDYLITIS: OBSERVATIONS ON THE INCIDENCE AND RESPONSE TO THERAPY AMONG VETERANS OF THE RECENT WAR \*

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THIS report deals with a series of 29 cases of rheumatoid spondylitis observed over a period of 15 months on the wards of a General Veterans Administration Hospital. Reports by several writers <sup>1,2</sup> have indicated that this disease has occurred among service personnel in a relatively greater ratio to peripheral rheumatoid arthritis than has been observed among the civilian population. Nevertheless we were not prepared for the number of cases encountered at a hospital not designated especially for the care of joint diseases. During the period under consideration there were 8,937 admissions to the hospital as a whole and 197 admissions to the wards set aside for the care of arthritic patients.

## CONTRIBUTORY FACTORS

*Age:* The average age on admission was 27.75 years with the youngest patient 21 years of age and the oldest 48 years. The average age at the onset of symptoms was 22.33 years with a range of from 10 to 30 years.

*Sex:* There were 29 males and 0 females. This ratio is to be anticipated in a veterans hospital, but it should be mentioned that the number of female patients encountered in such institutions is greater than one would expect.

*Race:* There were 26 white and three negro patients.

*Exposure and Infection:* Twenty-three cases were considered to be service connected, five cases developed the disease before entering the armed services, and in one case the service connection was undetermined. There were 25 who had been in the Army and four in the Navy. Four cases were precipitated by combat experiences and one while training for combat. Only four patients stated that symptoms began during periods of unusual exposure to cold and wet weather and none gave a history of any significant infection immediately preceding or occurring coincidentally with the onset of the disease.

*Trauma:* Eleven patients related trauma to their disability but in none was this of a severe or unusual nature. Two patients had falls of from 8 to 10 feet, one patient accused a lumbar puncture, another struck his back when wrestling, but in the remaining seven nothing more than the lifting and

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bending associated with the routine duties of a mechanic, munitions carrier or stevedore could be found.

*Geographical Factor:* For the most part rheumatic diseases have been associated with the temperate zones and cold wet weather recognized as a distinct contributing factor. In this group, however, 10 of the cases described their symptoms as beginning while they were stationed in the tropics or subtropics. Three were located in Hawaii, one in Panama and the others scattered about the South or Southwestern Pacific in such places as the Fiji or Sovereign Islands, New Caledonia or Guadalcanal. All of these regions were warm or hot, but had in common a heavy rainfall and were prone to be damp and cool at night. Fifteen cases noted the onset of symptoms within the United States in areas ranging from Georgia to Washington state and from Louisiana to Illinois. One patient developed the disease while on duty in the desert region of Southern California. In one instance the disease began in Iceland and in another while in Germany.

#### SYMPTOMATOLOGY

*Pain and Stiffness:* Pain is the universal complaint of patients with rheumatoid spondylitis and so was found to be the major complaint in each of the patients of this series. At the onset the pain is usually localized to the lower back, is often sharp and stabbing in character, intermittent in occurrence and tending to be more severe at night. Occasionally it may radiate into the lower extremities along the course of the sciatic nerves or around the lower trunk or chest. As the disease progresses the pain becomes more constant and severe with the patient noting progressive stiffness first of the lower back and later of the entire spine with the hips or shoulders often involved. As the stiffness progresses the pain frequently diminishes in intensity although a dull aching discomfort usually persists and acute exacerbations of pain due to minor stresses and strains are frequent.

Secondary symptoms such as insomnia, anorexia, and weight loss are common. The average weight loss in this group was 18 pounds with variation from no loss to a loss of 46 pounds. Discouragement, frustration, and severe mental depression were frequently encountered and one patient attempted suicide by drinking lye, which succeeded in complicating his already difficult illness with a severe esophageal stricture.

*Mode of Onset:* The gradual and intermittent development of the symptoms in the early course of the disease leads to many difficulties in early diagnosis and consequently a delay in early treatment. In 23 cases the onset was of a gradual nature and in six abrupt. This circumstance, as much as any other, contributes to the difficulties in early diagnosis so that at the time of admission to the hospital the average duration of the symptoms was 58 months. Almost all of the patients felt discouraged and confused by multiple varied diagnoses and inappropriate and ineffective management. Only two patients had previously received roentgen-ray therapy.

*Sequence of Joints Involved:* Although the disease is primarily an involvement of the articulating surfaces of the spine, it must be recognized that occasionally it may begin in other joints. Twenty patients first noted symptoms in the lower back, five in the hips, two in the ankles and knees and one in the sternoclavicular joints.

### PHYSICAL EXAMINATION

*General Appearance, Posture and Gait:* The average patient has a tall slender physique and often shows evidence of moderate weight loss. On gross inspection the posture frequently appears unaltered, but on close examination of the back certain changes can be detected. There is a loss of the lumbar curve in most instances with definite spasm of the paravertebral muscle groups. Movement of the back in all directions is guarded and restricted and when attempting forward flexion the lumbar spine remains rigid and flat. More advanced cases show evidence of dorsal kyphosis, scoliosis, a tilted pelvis or a "frozen" depressed shoulder. The gait is always abnormal. The back is held rigid in walking and the patient constantly guards against motion in any direction. If the disease is extensive the neck is likewise restricted in motion and the entire body must be turned in looking from side to side. With involvement of the hips the gait becomes even more disturbed, and with ankylosis of the hips the patient is apt to become a complete economic loss.

*Impaired Motion:* Involvement of the sacro-iliac and apophyseal joints alters and restricts motion of the spine in all directions although this is most strikingly demonstrated in attempts at forward flexion. The average patient was able to reach to only within sixteen and one-quarter (16.25) inches (40.8 cm.) of the floor with a range of from 5.5 inches (14.03 cm.)<sup>1</sup> to 24 inches (61.2 cm.). Involvement of the costo-vertebral joints reduces the excursion of the thoracic cage and the average chest expansion was 1.5 inches (3.83 cm.) with variations of from .25 to 3 inches (.64 to 7.65 cm.).

*Joints Involved:* Thirteen cases showed involvement of the spine alone, in 12 cases the spine, hips and shoulders were affected, and in four patients the spine, hips, shoulders and multiple peripheral joints.

### LABORATORY STUDIES

There are no laboratory findings of a pathognomonic nature associated with this disease. Some few are of value as an aid to diagnosis, but for the most part studies of the blood, urine, spinal fluid, and blood chemistries are normal or have no positive diagnostic value.

*Sedimentation Rate:* This is probably the most helpful of all laboratory studies and is almost always increased. The average rate (Cutler) in this group was 26 mm. with variations of from 7 to 40 mm.

*Vital Lung Capacity:* Because of the reduced expansion of the thoracic cage and limited chest expansion this, as would be expected, is reduced. In

27 cases this averaged 72.3 per cent with a range from 50 per cent to 109 per cent of normal.

*Hemoglobin:* The average hemoglobin determination on admission was 13.5 grams with a range from 11 grams to 15.5 grams.

*Acid Phosphatase:* In five cases in which this examination was made the acid phosphatase was normal.

### ROENTGEN EXAMINATION

Roentgenographic changes are probably the most valuable single finding in the diagnosis of rheumatoid spondylitis. These changes are noted most often in the following areas:

*Sacro-Iliac Joints:* These are the most important joints to be examined and will almost always show a bilateral involvement<sup>3</sup> if the disease is present. This may vary from an early narrowing of the joint space with irregular bone proliferation and osteoporosis of the adjacent bone to complete ankylosis. Each of the 29 cases in this series showed bilateral involvement of these joints.

*Apophyseal Joints:* These joints are more difficult to visualize and special oblique views are necessary to demonstrate any change. Here again changes vary from narrowing of the joint space to complete ankylosis. Examination of these joints was used only rarely in this series of cases and could not be said to have done more than add confirmatory evidence.

*Spinal Ligaments:* Calcification of the anterior and lateral ligaments and of the ligamentum flavum is a common finding and may appear relatively early in the disease. Fifteen cases showed evidence of calcification in one or more of these ligaments.

### TREATMENT

Treatment of this disease is directed to the following objectives: (1) The general care of the patient, (2) the relief of pain, (3) the prevention of spinal deformities.<sup>4</sup>

*General Care of the Patient:* Since there is no specific therapeutic approach, measures are necessary to enable the patient's own natural resistance to combat the lesion. These measures consist of adequate rest and a high caloric diet supplemented with vitamins. Of equal importance is the necessity of quieting the patient's apprehension about himself and his disease and restoring his morale. This is accomplished by a simple explanation of the nature of the disease and a prognosis couched in as optimistic fashion as the circumstances allow.

*The Relief of Pain:* At the present time the use of a penetrating roentgen ray (190 K. V.) directed over the back has proved to be the most effective measure in controlling the pain in rheumatoid spondylitis. Almost from the time of the discovery of the roentgen-ray this form of treatment has been used in a variety of modifications.<sup>5, 6, 7</sup> The technic generally used today,

however, is that advocated by Smyth, Freyberg, and Lampe in 1941.<sup>6</sup> This consists of dividing the spine into four areas and giving a total of 600 R in three to four doses at intervals of from two to four days. The schedule of treatment is so arranged that alternate areas are treated at the same time.

In the cases reported here the technic which has been employed is outlined in table 1. Treatments are given at biweekly intervals for two weeks until each area selected for treatment has received 600 R and the patient is allowed a rest interval of from six to eight weeks and the course is repeated. The average patient receives a total of three courses in this manner and then further treatment is withheld for six months unless a relapse occurs. At the end of six months the patient returns for reëvaluation and treatment is repeated or withheld according to his response.

The mode of action of roentgen-rays in relieving pain in rheumatoid spondylitis is not understood, but apparently its greatest beneficial effect results from its ability to lessen muscle spasm.

TABLE I  
Treatment Technic

1. Spine or back in four areas.
  1. Sacro-iliac 20×20
  2. Lumbar 10×15
  3. Dorsal 10×15
  4. Cervical 10×10
2. K.V. 190 M.A. 20 T.S.D. 50 cm.  
     .5 mm. copper —Filter  
     1.0 mm. aluminum
3. Dose: 150 R×4=600 R.  
     1 course per area.

Reaction to roentgen-ray therapy is fairly common and 75 per cent of our patients noted nausea, anorexia, or general malaise in varying degrees during treatment. In no instance was this of serious consequence and in no case prevented the completion of the full course of therapy. In one case not included in this series the leukocyte count dropped sufficiently low to warrant discontinuing treatment.

Other measures used to control pain are the free use of analgesics such as acetylsalicylic acid, phenacetin or sodium salicylate. In no case was it found necessary to resort to the use of a narcotic.

*Correcting Deformities:* The importance of a proper posture is stressed and all patients are instructed in exercises designed to maintain a normal posture and to strengthen the back muscles. Deep breathing exercises are given three times daily to increase the excursion of the thoracic cage. Since much of the early treatment of rheumatoid spondylitis is carried out with the patient confined to bed, it is important that his back be strengthened and supported during this period. This is best accomplished by the use of a

thin cotton or felt mattress supported on fracture boards which must extend under the entire length and width of the mattress. Only a small pillow should support the head. For 30 minutes each day the patient lies with a small pillow or sandbag under the lower dorsal area in order to hyperextend the spine.

An attempt is made to dispense with the use of any artificial type of support unless necessary to control a progressing deformity or to control pain not satisfactorily relieved by roentgen-ray therapy. If a support is necessary, the Taylor back brace or a "Three Point Brace" <sup>4</sup> utilizing a rectangular support across the sternum are the types most often used. Frequently a simple sacro-iliac belt is sufficient to control persistent low back pain. The use of traction in hip involvement with severe muscle spasm was a very useful procedure in two cases and the use of manual manipulation followed by the application of a cast served to establish a wider range of motion in one case with a "fixed" shoulder.

### THE RESULTS OF TREATMENT

Twenty-eight patients were treated with roentgen therapy.

*Relief of Pain:* Nineteen cases (67.9 per cent) reported a definite relief of pain and were improved by the treatment. In seven of these the results were excellent with no discomfort while at rest or on moderate use of the back. Statements to this effect were further qualified by the fact that sleep was uninterrupted and that analgesics and back supports could be dispensed with. Twelve patients reported a substantial relief of pain and were classified as good results. In these there was slight residual discomfort, sleep was occasionally interrupted and the patient still relied to some degree on analgesics and back supports or braces.

Nine cases reported no relief of pain or relief of such a minor degree as to be classified as unimproved.

Any attempt to evaluate a symptomatic response to treatment is difficult. There has been reason to believe that improvement has been definite in the cases cited because of the high incidence of returns for the completion of the treatment schedule. Each patient is discharged to his home between courses and in some instances this amounted to travelling from 500 to 700 miles. Nineteen patients have returned for two or more series of therapy; two receiving four courses, 10 receiving three, and seven receiving two.

*Other Results:* It has been emphasized by others <sup>6, 7</sup> that whereas roentgen-ray therapy is a valuable agent in relieving pain, it has not been of value in directly affecting the cause of the disease or of arresting the pathologic process. Some writers <sup>7</sup> have noted an improvement in the sedimentation rate although this has not been our experience to any striking degree. The average sedimentation rate on admission was 26.0 mm. and at the time of discharge 23.1 mm. Probably as a result of the relief of pain associated with an improvement in appetite and uninterrupted sleep there was a slight aver-



age weight gain with an increase from 143.75 lbs. on admission to 150.75 at the time of discharge. So far as the relief of stiffness is concerned the results are not impressive. This applies to the thoracic cage as well as to the spine proper. On admission the average range of flexibility was to within 16.25 inches (40.8 cm.) of the floor and at discharge to within 15 inches (38.25 cm.). The average chest expansion on admission was 1.5 inches (3.83 cm.) and remained unchanged after treatment. The average vital lung capacity before treatment was 72.3 per cent and after treatment 73.1 per cent.

### SUMMARY

Rheumatoid spondylitis is a disease of unknown etiology capable of producing severe crippling deformities and is particularly prone to affect otherwise healthy young males. Information gained from these observations and from reports published elsewhere indicate that its incidence is increasing. Precipitating factors such as trauma, exposure, infection and climatic conditions are variable and inconstant and knowledge about the cause and pathogenesis of the disease is inadequate. Roentgen therapy is a valuable means of controlling pain and relieving muscle spasm, but must be combined with measures of a general supportive nature and with measures designed to prevent or correct deformities. This plan of treatment appears as the most satisfactory available at the present time.

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## DIABETIC INDIGESTION \*

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DYSPEPTIC symptoms occur at times in diabetic patients and are related to the lack of control of the diabetes. We have seen a number of patients complaining of indigestion who, on examination, have shown only glycosuria and hyperglycemia to be present. Some of these patients were known diabetics, who at the time of examination were poorly controlled, others had never been diagnosed as having diabetes mellitus. The symptom encountered most commonly in these patients was a true pain in the epigastric region or across the upper abdomen. It varies in severity, sometimes being only a pronounced distress, but it is usually continuous and independent of meals. It is only slightly relieved by alkalis or sedatives. With severe acidosis, the clinical picture may simulate that of an acute surgical abdomen, which is not suggested in what we have designated as a diabetic indigestion. Other complaints encountered in these simple indigestion cases include post-meal distress consisting of pyrosis, bloating, belching and fluid regurgitation. Usually the appetite is good. Thirst is not complained of because polyuria is not present or pronounced enough to be noticed. The purpose of this paper is to present a description of a subjective type of indigestion in an individual who has a mild grade of diabetes mellitus and the dramatic result on the digestive symptoms of treatment directed toward the diabetes.

*The Abdomen in Diabetes.* The evaluation of abdominal complaints in the presence of diabetes mellitus must be circumspect, because for reasons which are still obscure, they occasionally differ from similar complaints in the non-diabetic. Abdominal complaints occurring in a diabetic person may be conveniently classified into three broad groups:

1. *The Acute Abdomen of Diabetic Acidosis.* A diabetic patient in acidosis may present the clinical picture of an acute abdomen. Bothe and Beardwood<sup>1</sup> reported a series of 136 cases of diabetic acidosis in which 96, or 74 per cent, presented the abdominal symptoms of nausea, vomiting and abdominal pain, usually associated with leukocytosis and fever. In the same series the remaining 26 per cent had central nervous system symptoms of drowsiness and coma. The abdominal symptoms rapidly disappear when the acidosis has been overcome.

2. *Organic Diseases of the Abdomen Occurring in a Diabetic.* In general, the clinical picture and laboratory findings in this group are similar to like conditions occurring in other patients. However, some observations should be noted. Acute abdominal infections may not produce as severe

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symptoms in diabetics as in non-diabetics under similar conditions. Severe abdominal infections may occur in diabetics without the presence of acidosis. Elsewhere in the body, infections occurring in diabetics are usually associated with an acidosis.

*Stomach.* Almost one-third of a series of 399 diabetics had a complete anacidity.<sup>2</sup> The incidence of peptic ulcer in a series of 12,000 diabetics was 94 cases or only 0.98 per cent.<sup>2</sup> In over half of these the typical ulcer syndrome was absent. In only 12 per cent was the HCl over 40° and in 67 per cent there was either no free HCl or it was below 20°. Severe complications of peptic ulcer in diabetes are unusually frequent. In the series cited above, massive hemorrhage occurred in 26.6 per cent, obstruction in 34 per cent and perforation in 10 per cent. Gastric carcinoma occurs somewhat more often than in non-diabetic ulcer patients..

*Liver.* Hepatic enlargement has been noted in patients with diabetes.<sup>3</sup> The diabetic is prone to fatty infiltration of the liver<sup>3</sup> and to depletion of the liver glycogen.<sup>5</sup> Diabetes is associated, frequently, with disease of the liver as evidenced by the presence of a strongly positive colloidal gold reaction. Hepatic involvement is much more prevalent in severe than in mild diabetes.<sup>4</sup>

*Gall-Bladder.* Diseases of the gall-bladder occur more commonly in the diabetic than in the general population and about one in four diabetics have gall stones at autopsy.

*Pancreas.* Impaired external secretion of the pancreas may be found in diabetics with diarrhea. However, in most diabetics digestion and absorption of foods seems to take place normally.<sup>6</sup>

3. *Diabetic Indigestion.* These patients usually have a mild diabetes which is either not diagnosed or is poorly controlled. Acidosis is usually absent. Their complaints of abdominal symptoms and digestive disturbances are prolonged in character and are rapidly relieved by proper control of the diabetes. As previously mentioned their complaints include: Upper abdominal pain, pyrosis, bloating, belching and fluid regurgitation following meals.

This last group is the one with which we are particularly concerned. Often the patient has been subjected to exhaustive laboratory studies to determine the reason for the complaints and little concern has been evidenced over a mild glycosuria and a slightly elevated blood sugar with no acidosis. Yet, when the diabetic situation has been better controlled, by diet alone or by diet plus insulin, the digestive disturbances disappear. No satisfactory explanation of this phenomenon has been advanced to date. Why some diabetic patients should have digestive complaints while others do not is difficult to explain, as are acute abdominal symptoms seen in diabetic acidosis. The severity of these digestive disturbances does not seem to be related to the severity of the diabetes.

The following case reports illustrate the condition above described as diabetic indigestion.

## CASE REPORTS

*Case 1.* A 61 year executive, first seen in 1946, had complained of indigestion, consisting of constant epigastric distress unrelated to food for about one and one-half years. He also had intermittent attacks of colicky epigastric pain which on two occasions necessitated opiates by hypodermic. The clinical diagnosis of biliary colic due to stones was made. These attacks of pain occurred at about three month intervals. His last attack had occurred about one month before he was seen. He had been hospitalized at that time and the physical examination was reported to be unremarkable except for moderate epigastric tenderness. The urine was reported as normal. An electrocardiogram was normal. After his ingestion of opaque dye, the gall-bladder was not visualized nor were any calculi evident. He was advised to have his gall-bladder removed. When seen by us one month later he still complained of epigastric distress but no severe pain. Physical examination was normal. Blood pressure 146 mm. of mercury systolic and 86 diastolic. There was a glycosuria with no acetone bodies. Fasting blood sugar was 162 mg. per cent. With diet alone the blood sugar level came down to 112 mg. per cent and the glycosuria disappeared in about three weeks. During the second week of treatment all symptoms of pain and indigestion gradually disappeared and have not recurred for a year to date. It is possible that this patient had a diseased gall-bladder, but it was not responsible for his symptoms.

*Case 2.* A 75 year old female had been a patient for 32 years. At the age of 28 she had an ovary and an intramural uterine fibroid removed. She continued to menstruate for six years and went into the menopause at 34. At 38 she had a cholecystectomy for gall stones. Since then she had occasional attacks of indigestion consisting of colicky pains, pyrosis, regurgitation of acid fluid from her stomach and also constipation. She was seen at irregular intervals for minor complaints. Her urine was always negative for glucose. She was not seen during the years 1929 to 1944. In 1944 she complained of swollen, reddened and itching vulva. Her urine was positive for glucose, no acetone was present and her fasting blood sugar was 189 mg. per cent. She did not complain of indigestion at this time and stated that she had been free of it for a number of years. With a moderately restricted carbohydrate intake and low fat diet plus 10 units of insulin per day, the vulvar condition rapidly cleared. Being satisfied with her improvement and general state of health, she became careless about her diet. Some six months later, indigestion occurred, beginning one evening with an acute attack of pain in the upper abdomen, slight fever (101° F.) and a leukocyte count of 14,200. The differential count was not especially significant. The physician in charge diagnosed her condition as an acute cholangitis and advised operation. She was brought to New York City at which time she complained of indigestion and a continued pain in the upper abdomen. Her temperature and blood count were normal. There was glycosuria and the ferric chloride and sodium nitroprusside tests were positive. The fasting blood sugar was 210 mg. per cent. After a complete examination, no cause for the abdominal complaints could be discovered. With insulin and diet her urine cleared and her fasting blood sugar came down to 130. She was placed on a diabetic regimen plus 40 units of protaminc zinc insulin. What is interesting is that as the diabetes was controlled, the sedatives and opiates could be dispensed with, and the pain and indigestion disappeared. She has now been free of digestive complaints and abdominal pain for two years.

*Case 3.* A banker, 38 years of age, had an appendectomy in 1931. Because of an attack of jaundice in 1941 he had his gall-bladder x-rayed and was told it was diseased. A month later it was reexamined and he was told that he had a "sluggish gall-bladder." He stated that he was all right if he restricted sugars and starches in his diet. When he went into the Army, he ate everything and had only one attack of pain which was promptly relieved by an injection. In February 1947 he began to

have epigastric pain, usually occurring in the late afternoon and accompanied by a sensation of pressure in the upper abdomen. He stated, "I have a big appetite, am thirsty and pass more urine than in previous years and have some insomnia recently." Although he had several urine examinations in the past, the presence of glucose had never been mentioned. At the time of examination in May 1947 there was glycosuria with no acetone bodies. Fasting blood sugar was 150 mg. per cent. With diet alone his blood sugar gradually came down to 90 mg. per cent and the urine was sugar-free. For the past six months he has felt well and has had no abdominal complaints.

*Case 4.* M. P., a 58 year old male truck driver with a non-contributory past history, began complaining of upper abdominal pain in 1946. At times the pain was severe but it had no relationship to meals or type of food. He had been diagnosed as having a peptic ulcer. Under treatment the pain persisted continuously for 10 months. He stated that he was fatigued and "too weak to work." He had insomnia and occasional attacks of diplopia. He "loves sweets," had a good appetite and lately passed a "good deal of urine." He was about 26 pounds overweight. His blood pressure was 150 mm. of mercury systolic and 86 mm. diastolic. General physical examination was negative. There was glycosuria with no acetone bodies. Fasting blood sugar was 170 mg. per cent. With diet plus 20 units of protamine insulin a day the diabetes was easily controlled and he began to feel much better. As the symptoms of diabetes disappeared, his digestive complaints abated. For over a year, with moderate increase in carbohydrate and 20 units of protamin insulin, he has had no indigestion and has been working steadily.

*Case 5.* A man of 74 was referred by Dr. Bejak of New York in June 1946. Six months before he suddenly got a "tremendous" pain in the abdomen, which a physician in the country where he lived said was due "to a cold in the kidneys." This pain, while less intense, had never disappeared since it started. He described it as a pulling sensation across his upper abdomen especially in the "pit" of his stomach. He had no other abdominal symptoms. His general condition was good except for a moderate hypertension (blood pressure 190/90). The urine contained glucose and a trace of albumin. The fasting blood sugar was 183 mg. per cent. The gall-bladder was static, retaining the dye over 48 hours. No stones were visualized. A moderately spastic colon was also noted. Being about 20 pounds overweight, hypertensive and diabetic, he was placed on a low fat diet with restricted carbohydrates. In a week he lost four pounds but glycosuria persisted. He was given 20 units of insulin a day and at the end of the third week he had lost 10 pounds, the urine was negative for both glucose and albumin and there was a reduction in the systolic blood pressure of 20 mm. of mercury. The abdominal pain disappeared four days after insulin was begun. The patient was seen one and a half years after initiating treatment for the diabetes and he states, "he feels perfectly fine in every way."

### COMMENT

All of these cases illustrate one important point, namely, proper control of the diabetes also controlled the digestive complaints. In a patient with abdominal complaints of a digestive nature in whom glycosuria is discovered, it is well to postpone evaluation of the abdominal situation. Attention should be directed toward accurate diagnosis and adequate treatment of the diabetes. When the diabetes is well controlled, in more than half of the cases we have seen, the digestive disturbances have disappeared completely. With persistence of the original complaint, a further investigation should be conducted to discover the cause of the indigestion. Another point which

should not need to be emphasized is that every patient who complains of digestive disturbances should have a urinalysis. As Joslin<sup>2</sup> puts it "don't depend on symptoms for diabetes. Diabetes will not be found without search." Some obscure abdominal complaints are caused by diabetes and are readily amenable to its treatment.

### SUMMARY

✓ Digestive disturbances, relatively mild in nature but present over long periods of time are occasionally encountered in mild cases of diabetes.

Often the underlying diabetic state is not discovered or considered significant and the patient presents a puzzling picture.

The condition which we have presented as diabetic indigestion does not appear to be due to an acidosis or to any organic condition. Treatment directed toward proper control of the diabetes rapidly relieves the patient of all digestive disorders. If symptoms persist after the diabetes is controlled, search elsewhere for the cause of the indigestion is in order.

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# SOME UNUSUAL OBSERVATIONS IN POST TRANSFUSION REACTIONS: TWO CASES WITH AUTOPSY FINDINGS \*

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THE renal pathologic lesion following hemolysis of transfused blood has been described many times (Bordley,<sup>1</sup> Goldring and Graef<sup>2</sup>; DeGowin, Warner and Randall<sup>3</sup>; Dardinski<sup>4</sup>; Payne<sup>5</sup>; Witts,<sup>6</sup> among others). Lesions of other viscera have also been observed, but reported less frequently (Bordley, Goldring and Graef; Dardinski).

The relationship of intravascular hemolysis to the resulting renal disease and lesions of other viscera does not appear to be clear. Indeed, some difference of opinion still exists relative to the pathogenesis of the so-called transfusion kidney.<sup>3</sup>

The two cases to be reported herein because of marked differences in the duration of life after the transfusion time-interval before death, yet with practically identical necropsy findings, may permit certain deductions.

## CASE REPORTS

*Case 1.* Mrs. V. T., a white woman of 32, was admitted to the Woman's Medical College Hospital on July 8, 1943. The presence of fever, joint swelling and pain, leukopenia, palpable liver and spleen, and the development of skin lesions over the forehead and "butterfly" area, were indications of acute lupus erythematosus. This was confirmed by the dermatologist, who suggested, among other things, repeated small blood transfusions.

On the evening of July 20, 250 c.c. of blood were administered over a period of one and one-half hours. At the end of this time, the patient had severe chills, vomiting, incontinence of urine, and a rise in temperature to 105.4°. She felt improved after 3 minims of adrenalin. There was slight cyanosis but no pitting edema.

At 1:30 a.m., July 21, the patient began to vomit and seemed in critical condition. She was staring blindly into space with pin-point, non-reactive pupils. She responded only by a flicker of her eyelids to her name, and began to have bilateral convulsive movements. Her pulse was imperceptible at the wrist, blood pressure was 60 mm. Hg systolic and 26 mm. diastolic, respirations very labored and occasionally almost Cheyne-Stokes in character. Shock treatment was given—plasma, cortin, shock blocks, and 1000 c.c. sodium lactate (slowly, by vein). Blood pressure rose to 84 mm. Hg systolic and 50 mm. diastolic, the pulse and respirations improved, but the patient remained entirely unresponsive. About 6:20 a.m., blood pressure 90 mm. Hg systolic and 40 mm. diastolic, and 3 c.c. of cortin were given intravenously, during which respirations ceased. Patient responded briefly to coramine and metrazol, but died at 6:50 a.m. Death occurred about 12 hours after transfusion. (Laboratory data table 1.)

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*Autopsy Findings: Gross Description: General:* Body is that of an obese white woman about 35. Lips and nails are blue. Skin is yellow; sclerae are clear. Breasts appear normal. There are the following lesions in the skin: (1) On cheeks and bridge of nose dusky red, fairly well demarcated areas of edema, larger on right cheek. (2) On midforehead at hairline is a reddish area which centrally is covered with fine dry scales, similar lesions on neck. (3) Small dull red papules on trunk and arms, larger ones on legs showing small ulcers. (4) Small blue linear scar on right scapula. (5) Slightly depressed circular scars below right clavicle, on sternum and in lumbar region. (6) Hair, especially in occipital region, and skin of neck covered with greasy scales. Diaphragm: left dome at fourth interspace; right at third interspace. Serous cavities: *Pericardial* cavity is normal. *Pleural* cavities: left appears normal, right contains about 300 c.c. of clear fluid; there are scattered fibrous adhesions on lower lobe. *Peritoneal* cavity: there is no dilatation of vessels in splanchnic area; no fluid in cavity. *Aorta:* there are a few small areas of atheroma in ascending aorta. *Heart:* Weight 290 gm. Diameter in situ: oblique 12.5 cm., vertical 8 cm., diaphragmatic 6.5 cm. Right ventricle is moderately dilated in region of conus; muscle is pale; wall 3 mm. thick. Left ventricle appears normal in size, muscle is firm and pale yellow; wall 17 mm. thick. Valves: circumference—tricuspid 9.8 cm., pulmonary 7 cm., mitral 8.3 cm., aortic 6.5 cm. Valves are free from verrucae and fibrous thickening. Coronary arteries appear normal. *Lungs:* Weight: left, 520 gm.; right, 500 gm. There are petechiae in pleurae, especially of lower lobes. Organs are relatively heavy, subcrepitant in lower lobes. On section the upper lobe of left lung retracts and is red; the lower lobe does not retract, is dark red. On section the upper and middle lobes of right lung are pale and exude a moderate quantity of slightly blood tinged fluid. Lower lobe is like that of the left. *Lymph nodes:* There are several slightly enlarged nodes in superior mediastinum. Retroperitoneal nodes are moderately enlarged. Their consistency is only slightly increased; on section they are dark red. There is a small mass of calcified nodes in mesentery. *Spleen:* Weight: 520 gm. There is a small accessory spleen. Fibrinous adhesions on upper pole of spleen. A fairly deep fissure crosses phrenic surface of upper pole. On section: dry, brownish red; there are several slightly raised nodules about 4 mm. in diameter, paler than cut surface generally; there are smaller nodules which are believed to be Malpighian bodies. *Kidneys:* Weight: left 210 gm.; right, 180 gm. *Left:* Petechiae are seen in capsule. Capsule strips easily. Outer surface is smooth. On section cortex is pale brown and on average is 7 mm. in width. Medulla is well demarcated and averages 15 mm. There are minute hemorrhages in mucosa of pelvis. *Right:* Is similar, but is moderately congested. *Ureters:* Appear normal. *Bladder:* Appears normal. *Genitalia:* Uterus and appendages appear normal. There is a recent corpus luteum in right ovary. *Gastrointestinal Tract:* Stomach: in the mucosa are a few petechiae near cardia. Small intestine: calibre throughout this part of the gut is extremely small; there are scattered hemorrhages in mucosa. Colon appears normal. There is a small hemorrhage in mucosa of appendix. *Liver:* Weight is 2400 gm. In situ lower border is 6 cm. below CM in right mid-clavicular line, 9 cm. from ensiform. Borders are rounded. Outer surface is smooth and pale except for dilatation of capsular venules on lower border. On section surface is uniformly yellow. *Gall-bladder and ducts:* Appear normal. *Pancreas:* Appears normal. *Adrenals:* Appear normal. *Brain* is free from congestion, edema, and hemorrhages.

*Microscopic Description: Heart: Left Ventricle:* The most striking features are extreme edema and extreme degeneration of the muscle fibers. Cross striation is very faint, irregular, and sometimes absent. The myofibrils appear separated by edema in many of the cells. When seen longitudinally most of the fibers are frayed at their ends. Fragmentation is present, but there is so much separation of cells by



edema that the gaps are much wider than normal. The nuclei are generally pyknotic. There is no obvious hypertrophy although some of the nuclei are very large. The blood vessels are dilated but contain very few red cells. The endothelial cells are often considerably swollen. Around the vessels are spaces apparently due to edema in which a fine fibrin meshwork is visible. Fibroblasts are seen here and there and slight infiltration with mononuclear and plasma cells. Here and there the infiltration assumes the proportions of a "node." In these nodes are cells with branching protoplasm, evidently histiocytes, and other cells whose protoplasm is difficult to see but is also apparently branching and whose nucleus resembles that of an Aschoff cell.

*Lungs:* Right: Right lung is congested and shows alternating areas of collapse and emphysema. The alveolar walls are considerably thickened, and this is true even in the emphysematous areas. The thickening is due mainly to enormous dilatation of the capillaries and to some extent to the presence of large mononuclear cells. Some of the alveoli contain a scanty exudate of mononuclear cells with a few very large scavenger cells, a small amount of fibrin and a few red blood cells. Occasionally a giant cell is seen. Scattered over the lung substance are tiny nodes consisting of lymphocytes intermingled with a cell of the histiocyte type which resembles an endothelioid cell. These nodes are situated sometimes near arteries, sometimes in alveoli and do not appear to have any connection with the normal lymphoid tissue in the lung. The bronchi show some desquamation of the epithelium, hypertrophy of the smooth muscle and intense congestion of the vessels of the submucosa. Most of them do not contain exudate.

*Left: (Lower lobe:)* The tissue stains poorly and appears more or less necrotic. All the alveoli are filled with pale, slightly granular material in which large numbers of bacteria are visible. These may be contaminants. The blood vessels contain large numbers of mononuclear cells. Fibrin is seen in many places both inside and outside the vessels. Nodules resembling those described for the right lung are present here also, except that they contain giant cells and pigment bearing cells. Many of them are seen close to large vessels.

*Spleen:* The walls of the sinuses are greatly thickened and there is considerable edema of the tissue as a whole. The cells lining the sinuses are swollen, large phagocytic cells are found in several places, also giant cells with two or more large nuclei. The Malpighian bodies are edematous and germinal centers apparently absent. Some of the Malpighian bodies are necrotic. One or two nodes similar to those seen in the lung are visible although they are somewhat difficult to distinguish from normal structures in the spleen. Occasional necrotic foci are found in the pulp.

*Right Kidney:* There is marked edema of the medulla together with disintegration of many of the collecting tubules. The rest of the kidney shows little or no edema. The Malpighian bodies are swollen, the loops are plump. The capillaries are open, some contain blood, others appear empty. There is moderate desquamation of the epithelial cells with swelling of those that remain. The endothelial cells are slightly swollen and stain deeply. The capsular space is moderately distended, the lining cells are slightly swollen, sometimes desquamated. Occasionally they show slight proliferation, similar to very early crescent formation. The convoluted tubules are a little dilated, the lumen contains granular material, the lining cells are somewhat granular, and sometimes disintegrating, but in many a brush border is still seen. The lesions appear most severe in the distal convoluted tubule and the loop of Henle. No casts are found in the tubules. In the fascia near one of the large arteries is a group of lymphocytes with a few histiocytes. It is uncertain whether this is a lesion of lupus erythematosus or merely a group of lymphocytes such as is often seen in the kidney.

*Liver:* The liver cells show large and small vacuoles. When not vacuolated the protoplasm is extremely granular. The outlines of the cells are sometimes indistinct. Some of them are completely necrosed. The liver cells are so distorted that it is difficult to make out whether the general architecture is altered. However, except for necrotic foci, the

distortion seems to be due to the swollen liver cells which compress the sinusoids so as to render them invisible. When sinusoids are seen there is a wide Dissche space containing fine fibrinous threads. The portal spaces are also edematous; they contain scattered mononuclear cells. Here and there in the liver are nodes like those seen in the lungs. They contain large and small lymphocytes, plasma cells, histiocytes and occasional eosinophiles, a fine reticular network and sometimes remains of liver cells. Somewhat similar formations are seen surrounding and enclosing groups of liver cells in the same way as fibrous tissue does in cirrhosis. This tissue is sometimes connected with portal spaces. The larger vessels, especially the veins, are dilated but they contain very few red cells. Some contain fibrin. *Lymph Nodes*: The first section shows remarkable general edema of the nodes with almost complete absence of germinal centers, considerable dilatation of the blood vessels, much less of the lymph vessels. The vessels here contain red cells. Lymphocytes are scattered evenly through the gland. Pigment bearing cells and occasional giant cells are seen. The reticulum cells are swollen. Hemorrhage is present here and there. A typical granulomatous node is seen near the center. The other node is similar but shows some indication of germinal centers. The vessels are dilated but empty; lymph sinuses are also dilated. Numerous pigment bearing cells are seen. *Adrenal*: Section shows edema, lack of cortical lipid and occasional small necroses.

*Case 2.* Mrs. L. L., a white housewife of 55 years, was admitted to the Woman's Medical College Hospital on June 10, 1943, for a three-stage left thoracoplasty because of bilateral chronic pulmonary tuberculosis. The first and second stages were done on June 15 and June 29, respectively, without incident.

On July 13 the third stage muscle-splitting thoracoplasty was performed. The patient's condition was good until the end of the operation, when her breathing became labored and her blood pressure dropped. She was given 500 c.c. glucose in saline and 150 c.c. blood. Through an error 150 c.c. of type 3 blood were given instead of the type 2 required. There was no chill, blood pressure remained on the same level for a short period of time. Intravenous 5 per cent glucose in saline was started as soon as error was noted, while waiting for plasma to be melted. Patient's blood pressure and pulse became barely perceptible and she went into marked shock. (Blood pressure was about 60 systolic.) She was given 500 c.c. compatible blood and continuous 5 per cent glucose in saline slowly as well as adrenal cortical extract 2 c.c. per hour. It was necessary to redress the wound twice because of hemorrhage. In the evening the blood pressure went up to 108 mm. Hg systolic and 66 mm. diastolic (at the beginning of the operation the blood pressure had been 110 mm. Hg systolic and 80 mm. diastolic). *July 14*: The patient has voided three times since operation and was catheterized three times; only small quantities (75 to 150 c.c.) of urine were obtained but the patient's condition seemed much improved. *July 15*: Yesterday's total fluid intake was 3500 c.c., the total output 850 c.c. Patient was placed on potassium citrate in hope of redissolving the acid hematin crystals which might be in the kidneys. Five hundred c.c. m/6 sodium lactate given intravenously to alkalinize urine. Watermelon was given for diuresis. Late in the evening potassium citrate was replaced by  $\text{NaHCO}_3$ , because of possible toxic effect of the K-ion. Today's output practically nil—100 c.c. for 12 hours. *July 16*: Blood urea nitrogen rising, icterus index normal (see table 2). Urine loaded with crystals. Blood count is given in table 2. Temperature graph is flat, and there is great subjective improvement. No edema. Another 500 c.c. 10 per cent glucose in distilled water. *July 17*: Yesterday's output 440 c.c.; intake inadequate—1910. 250 c.c. plasma and 1000 c.c. 5 per cent glucose in saline. Blood urea nitrogen is increasing. *July 18*: Fluid output was 1230 c.c. *July 19*: Blood urea nitrogen somewhat lower. However, patient complained this morning of impairment of vision. Ophthalmoscopic examination revealed arteriosclerosis but no changes characteristic of uremia. During the afternoon

TABLE I

Date	Sed. Rate	Red Bl. Cells	Hb. Gram	Hb. %	White Blood Cells	Poly.	Lym.	Mono.	Eos.	pH	Sp. Grav.	Alb.	Sugar	Leuk.	Erythr.	Casts	Epith.	Cryst.	Blood Sugar	Blood Urea	Ict. Index
7-9-43	12	3,550,000	9.5	64	3,150	76	22	1	1	5.0	1018	Light cloud.	0	0-1	0	0	2	Many	100	12	—
7-13-43	—	2,950,000	9.0	61	3,400	72	23	4	1	—	—	—	—	—	—	—	—	—	—	—	—
7-19-43	54	2,780,000	9.0	61	3,350	80	20	0	0	—	—	—	—	—	—	—	—	—	—	—	—
7-20-43										5.0	1015	Faint trace	0	10-15	0	0	Many	Bact.	—	—	—
7-21-43																					50

## Blood Culture:

7-10-43: No growth  
 7-15-43: No growth  
 7-19-43: No growth

## Slide Agglutination

7-10-43 } Negative for Typhoid H and O  
 7-15-43 } Paratyphoid A and B  
 Proteus X19  
*Brucella abortus*

## Stool Culture:

7-15-43: *Escherichia coli*, *Staph. aureus*;  
 hemolyt., coagulase negat.

## Urine Culture:

7-15-43: *Staph. aureus*; hemolyt.  
 coagulase positive.

the patient had several attacks of convulsions coming in short succession. The attacks witnessed by the interne were characterized by convulsions of the right arm and conjugated deviation of the eyes to the left.

*Neurological consultation* (Dr. Winifred B. Stewart)—essential findings: Impairment of vision, other cranial nerves normal. Biceps, patellar, triceps, Achilles reflexes all hyperactive, and perhaps right is greater than left, although this difference is not consistent. Babinski reflex is positive on right. Some weakness of right grip. All forms of sensation apparently intact. "In view of the impairment of vision and convulsions, uremia is the most likely cause of this condition. However, the fact that the convulsions are unilateral and also that the neurological findings tend to be unilateral suggest the possibility of a vascular lesion on left side."

*July 20:* Generalized subcutaneous edema and marked pallor are found, patient is markedly dyspneic. Râles are heard throughout the chest. The abdomen is distended but no free fluid found at examination. Blood pressure 128 mm. Hg systolic and 88 mm. diastolic. Comment of the medical consultant: "It is obvious that the patient is in very poor condition. It is probable that the fluid disturbance is on the basis of renal insufficiency. Whether the heart is contributing to the pulmonary congestion is questionable." *July 21:* Patient died.

*Autopsy Findings: Gross description: General:* Body is that of a well developed, well nourished white woman about 55. Lips and nails are blue. There is a thoracoplasty scar on left upper chest and a recent thoracoplasty incision in left scapular region; this wound is healed but the stitches have not been removed. Abdomen is markedly distended. There is a transverse incisional wound on dorsum of right foot. On extremities are many small circular depressed scars. *Diaphragm:* Left dome is at fifth interspace; right at third interspace. *Thoracic cavity:* The mediastinum is shifted somewhat to the left. Left lung is collapsed against the lateral and posterior wall. The voluminous right lung almost covers the mediastinum; on medial surface of upper lobe are small string-like adhesions to mediastinum. *Lungs:* Have been described in situ. Left lung was not removed because of dense universal adhesions. In upper lobe is a cavity about 4 cm. in diameter. Right lung weighs 540 gm. It is emphysematous. In the apex of upper lobe is a fibrocaseous nodule about 5 cm. in diameter; in the center is a recent cavity about 2 cm. in diameter. Also in this lobe are small healed tuberculous nodules; they are at site of adhesions described above. *Aorta:* There are small atherosclerotic nodules in the ascending aorta. *Heart:* Weight is 290 gm. In situ diameters are: oblique 12.5 cm., vertical 10 cm., diaphragmatic 5.5 cm. Right ventricle is moderately dilated; wall is 4 mm. thick. Wall of the left ventricle is 14 mm. thick. Muscle is pale brown and moist. Valves: circumferences are: tricuspid 12 cm., pulmonary 7 cm., mitral 9.5 cm., aortic 6.5 cm. Mitral valve: anterior cusp shows moderate atherosclerosis. Coronaries appear normal. *Spleen:* Weight is 125 gm. It is normal in consistency. On section surface retracts; it is pale red except for small areas of hemorrhage. *Kidneys:* Left is normal in weight and size. Capsule strips easily. On section the pale, bulging cortex is well demarcated from the medulla. Pelvis appears normal. Right kidney is large and of unusual shape. The extrarenal pelvis is enormously dilated and roughly pyramidal with apex at ureteropelvic junction. The kidney lies like a small cap over this dilated pelvis. It is remarkable that when ureter was cut the pelvis did not empty, but this phenomenon can be explained probably by the extremely small caliber of ureter at its beginning. When pelvis is opened the mucosa is found to be granular and the wall relatively thick. Calices are considerably dilated. *Bladder:* Appears normal. *Gastrointestinal tract:* Stomach is markedly distended, rugae are effaced. Transverse colon is also markedly distended. Sigmoid has a fairly long mesentery and is adherent to posterior surface of broad ligament. In the cecum there are many small acute ulcers. *Liver:* Weight is 1160 gm. In situ the lower border is 3 cm.

TABLE II

Date	Fluid Intake	Fluid Output	R.B.C.	Hb. %	W. B. C.	Stab.	Seg.	Poly.	Lymph.	Mono.	Eos.	Bas.	Turk	Urine								Blood Chemistry					
														pH	Spec Grav.	Alb.	Sugar	Bile	W.B.C.	R.B.C.	Casts	Epith.	CO <sub>2</sub> v	Total Protein	Urea N	Ict. Index	
6-10, 11			3,980	70	8,100			76	16	4	2	1	1	7.5	1010	0	0		10-15	0	0						
7-13			3,390	64	17,800																						
7-14	3,500	850	3,390	64	17,800	18	68	86	12	2	0	0	0						No. acid hematin crystals								
7-15			2,910	61														0	8/1 mm. <sup>3</sup> 1/1 mm. <sup>3</sup>					60			
7-16	1,910	440	3,440	69										7.5	1013	Cloud.			5-10	0	0				58	1.45	
7-17			3,530	67										7.5	1010	Trace	0		20-40	0-1	0			52	5.8	9	
7-18														7.0	1010	Trace	0		15-20	0-2	0	Few					
7-19			3,410	70										7.5	1007	Heavy trace	0		4-6	0	0	Many			51	20	
7-20																									66.5		
7-21														7.5	1009	Heavy trace	0		0-1	0	0	0					

Serology: Kolmer, Kline, neg.  
Sputum: Positive for acid fast bacilli (6-11-43).

above costal margin in right midclavicular line and 4 cm. below ensiform. Over the lower anterior surface of right lobe the capsule is thickened and surface granular. On section lobular pattern is distinct. *Gall-bladder and ducts*: Appear normal. *Pancreas*: Appears normal. *Adrenals*: Appear normal. *Uterus and appendages*: Appear normal.

*Microscopic Description: Heart*: There is everywhere marked separation of the muscle fibers by edema. Cross striation is remarkably well preserved. In longitudinal sections the fibers appear stretched and are joined by elongated bands in which a few fibrils are seen surrounded by vacuoles. This may be due to dilatation. The endothelial cells of the vessels in the connective tissue are swollen; fibrin and a few mononuclear cells are seen around them. In some places there is the appearance of interstitial myocarditis (serous inflammation). In cross section the muscle fibers are irregular in size, some are very large and vacuolated. *Spleen*: The spleen is amazingly bloodless. It shows slightly dilated sinuses, lined by swollen endothelial cells. The protoplasm of these cells is scanty and in some areas there is little or no evidence of phagocytosis, but in others the cells contain irregular pink material which seems to be derived from degenerated red cells. Malpighian bodies are present, but they are small and poorly defined. The arteries and arterioles are empty, the walls are edematous; in some of them hyaline material is seen in the intima. The fibromuscular trabeculae are also edematous. *Kidney*: Under low power the most striking change is extreme edema throughout the kidney substance. Here and there are groups of distended blood vessels, surrounded by inflammatory cells. *Glomeruli*: Bowman's capsule is everywhere somewhat dilated. The lining cells are partly shed; those that remain are swollen and pyknotic. Sometimes the capsular space appears empty, but more often it contains a fine fibrin-like meshwork in which appear what may be shadows of cells. This material usually lies against the capsule, but in some instances fine threads connect the glomerular loops to the capsular membrane. The first convoluted tubule where it opens into the capsule is filled with similar material. A similar fine meshwork lies in all the convoluted tubules. The material appears to become condensed at the loop of Henle. At the junction of the ascending and descending loops of Henle the material becomes more condensed and granular. In a very few loops it is seen as a pinkish granular mass. Some of the collecting tubules contain the material, but most of them are empty. Occasionally clumps of shed cells are found in the tubules, but true cellular casts are not easy to find. It is to be noted that nowhere, in any of the tubules, is there anything approaching a block. In fact, the tendency is for the tubules, especially the convoluted tubules, to be dilated. A notable feature of the glomerular tufts is that no blood is visible in the majority of them. It is hard to find even one red cell in the capillary loops. Occasionally the afferent arteriole empties into a lacuna, but in only a few of these lacunae are there red cells. The capillaries on the tufts are often dilated, although empty. Many of the capillary loops contain fibrin thrombi. Many of the epithelial cells are shed, leaving the loops bare. There seems to be little or no multiplication of the cells that remain. *Convoluted tubules*: The tubules are dilated, the epithelial cells are granular and partly disintegrated. Some cells are completely degenerated; remnants of a brush border are seen in others. The convoluted tubules are separated by a narrow zone of edematous connective tissue, in which a few fibroblasts are seen. Towards the medulla the tubules are smaller, their epithelium is similarly degenerated, and they are often widely separated by edema and also by fibroblasts. The inflamed areas which catch the eye on superficial examination of the section are arranged more or less regularly (?). Close examination of such areas reveals numbers of widely distended blood vessels (the only place in the kidney where dilated vessels are found), and between the vessels a cellular exudate in which remains of kidney tubules can just be made out. The exudate consists chiefly of mononuclear cells, but in it are also a

fair number of eosinophiles and occasional polymorphonuclears. Fibroblasts are fairly numerous and more in evidence than is commonly seen in kidney lesions. This is probably because it is unusual to obtain a kidney in such an early stage of inflammatory change. The arteries are remarkably normal for a patient of 55. The afferent arterioles are edematous and show swelling of the endothelial cells. The pelvic fat is infiltrated with groups of inflammatory cells, chiefly lymphocytes. There is also an area of hemorrhage. *Liver*: The liver cells show severe degenerative changes. The liver is dotted with necrotic foci. These are often peripheral in the region of sublobular veins, sometimes central, but are not found in connection with portal spaces. Apart from the areas of necrosis the liver architecture is preserved, but the cells are sometimes shrunken and breaking up, sometimes swollen, very granular with a sponge-like protoplasm, sometimes vacuolated or distended from fatty change. Here and there a small amount of bile pigment is found in the cells. Dissche's space, i.e., the space between the endothelium of the sinuses and the liver cells, is enormously distended. Fibrin threads are present in the space and in the sinuses. Blood cells are extremely scanty. In many places the Kupffer cells and the endothelial lining are destroyed. In most places Kupffer cells are rather hard to find, but when seen, are either very large or are in process of degeneration. In the necrotic areas, however, the Kupffer cells are abundant and filled with yellow pigment. They lie in a background of fibrin threads with occasional fibroblasts, and one or two mononuclear cells. The portal veins are distended but almost empty of blood, the periportal connective tissue is somewhat edematous; a few mononuclear cells are seen in it. The epithelium of the bile ducts is shed; the arterioles appear contracted.

*Anatomical Diagnosis*: *Heart*: Dilatation, edema; myocardial degeneration. *Lungs*: Thoracoplasty, pulmonary atelectasis, healed and active tuberculosis. *Kidney*: "Transfusion kidney." *Liver*: Focal necrosis. *Cause of death*: Hepatorenal syndrome due to incompatible transfusion.

## DISCUSSION

Both of these cases demonstrated severe generalized visceral edema with changes in the parenchyma of several vital organs (especially the heart, kidney and liver). Both cases showed marked alteration of the cells of the reticulo-endothelial system. The immediate cause of death was failure of the parenchymal organs. Both cases showed transitory cerebral symptoms before death.

It is of interest that the post-transfusion survival period in case 1 was a matter of hours; whereas, in case 2, it was longer than one week. Case 1 received only 250 c.c. of blood presumably compatible, although nothing is known concerning the titer of the serum used for testing.<sup>6</sup> Case 1 received 150 c.c. of incompatible blood (through an error in labeling). In both instances fatal reactions followed relatively small transfusions. This is at variance with the tendency to determine prognosis on the basis of the amount of reaction-producing blood transfused.<sup>11</sup>

Preëxisting reticulo-endothelial disease may have been a determining factor.

The speed of administration of blood in case 1 (something less than 3 c.c. per minute) does not appear to be an important consideration. There was no evidence of pulmonary congestion or edema at the onset of the reaction.

Moreover, prior to transfusion, there was no clinical evidence indicating a diminution of cardiac reserve incapable of supporting a greater load.

The cerebral symptoms might be attributed to renal failure in case 2, but this is impossible for case 1. However, the symptoms resemble the observations of Lehane<sup>7</sup> and of Robinson,<sup>8</sup> who saw transient blindness and temporary mental disorder appear a short time after blood transfusions. Lehane<sup>7</sup> indicates five possibilities for the explanation of this phenomenon but finds all of them wanting. The writers feel that edema of the central nervous system is the most likely cause, with cerebral ischemia due to or increased by hypotension as an alternate possibility.

The major symptoms at time of death were those of oliguria, hyposthenuria (especially in case 2), retention of urea, and evidence of icterus. Originally the picture of kidney damage after transfusion was ascribed to the blocking of the renal tubules by acid hematin precipitates.<sup>9</sup> However, there is no evidence of a block of the tubules in either case, and the purely mechanical explanation of anuria does not hold true. Baker and Dodds'<sup>9</sup> interpretation has found many opponents in recent years.<sup>10, 11, 3, 4.</sup>

The icterus, visible at autopsy in case 1 and well established by laboratory tests in both cases, can be explained on the basis of hemolysis or hepatocellular disturbance. Although in case 1 icterus appeared overnight, in case 2 it developed late (long after the hemolytic process could account for it). On the other hand the marked and widespread damage of the liver cells in both cases suggests an hepatocellular jaundice.

Furthermore, we are able to trace the development of the edema in case 2. The figures for fluid intake and output show that there has been hidden tissue edema as early as July 16, when the icterus index was still low. We may conclude, therefore, that—at least in the case of the liver—signs of tissue damage have *followed* the appearance of generalized edema. Since renal and hepatic symptoms coexist, from a clinical standpoint the term post-transfusion hepatorenal syndrome is permissible here.

Tissue parenchymal damage in its relation to edema has been studied by Eppinger and his associates,<sup>12</sup> who gave a new meaning to the old term of "serous inflammation." It is most common in the liver, but pathogenically similar lesions in the kidneys have been described.<sup>2, 6, 13</sup> Endogenous "capillarotoxic protein split products" have been held responsible for producing them. Such a mechanism seems to apply in the production of the visceral lesions observed at autopsy in these cases. The parenchymal lesions might well be considered the sequelae of tissue edema resulting in variable degrees of tissue anoxia with consequent capillary damage.

## CONCLUSIONS

The cases presented in this report show not only the renal pathologic lesions seen in post blood transfusion reactions and changes in the liver, but also generalized and widespread visceral and tissue edema. The findings



in case 1 indicate that this edema is not the result of renal failure, since sufficient time could not have elapsed for this development. Case 2 appears to fall into the same category, in view of the evidence of water imbalance causing hidden tissue edema noted long before failure of the kidney and liver parenchyma became clinically apparent. It is possible, if not probable, that the autopsy findings in these cases were conditioned by the preëxisting reticuloendothelial disease. Should this be the case, certain considerations become of paramount importance: (1) The symptoms are usually characteristic of renal disturbance, but clinical and laboratory evidence may reveal liver involvement. In this instance the term hepatorenal syndrome is permissible. However, the arrival at this conclusion should suggest that visceral (parenchymal) involvement may not be confined to the kidneys and the liver. It may involve other organs: heart, brain, and lungs. (2) The occurrence of widespread interstitial edema makes one wonder whether the usually recommended therapy in cases of hemolysis due to incompatible blood transfusion should be employed in cases such as those here reported. The forcing of fluids, especially where oliguria or anuria exists, would tend to increase tissue edema. It would seem to these writers that technics designed to prevent and control tissue edema would be desirable. Thus, plasma and, perhaps, hypertonic solutions, may be employed. The use of mercurial diuretics should be considered to mobilize extrarenal water. Substances capable of improving capillary function, such as ascorbic acid, adrenal cortex hormone, and calcium, may be employed with benefit.

### SUMMARY

1. Two cases of fatal transfusion reactions with autopsy findings are described.
2. Although death occurred in a matter of hours in one case and after one week in the other, the pathologic findings were similar. Widespread visceral edema was seen in both cases.
3. Transfusion reactions and death occurred after 150 c.c. of incompatible blood were administered in one case and 250 c.c. of blood in the other.
4. The patho-physiologic aspects are discussed. The possible effect of prior reticuloendothelial disease as a conditioning factor in the production of widespread visceral involvement in transfusion reactions is mentioned.
5. Changes in therapy are considered.

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# THE BEHAVIORAL RESPONSE OF PATIENTS SEIZED WITH AN ACUTE MYOCARDIAL INFARCTION \*

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THE clinical features associated with an acute episode of a coronary occlusion with myocardial infarction are so well known to the medical profession today that the diagnosis of this condition is usually made with ease on the basis of the history and physical examination. This has been due to the pioneering work of Herrick,<sup>1, 2, 3</sup> Dock,<sup>4</sup> Wearn,<sup>5</sup> and Levine<sup>6</sup> as well as others who were among the first to point out the essential symptomatology and physical findings upon which the diagnosis rests.

The purpose of this paper is to present an additional feature of the disease which may be of value in some instances in making a clinical diagnosis of this condition when it otherwise might be a matter of doubt or hesitation. The manifestation about which I wish to call attention is the instinctive response of the individual seized with a coronary occlusion to his pain. It is my belief that this response is one of effort, and that in this respect it differs from that which occurs in the symptom complex known as angina pectoris.

In angina pectoris the patient usually complains of an oppressive substernal or epigastric sensation which may radiate to the arms, neck, or back. This pain comes on after effort or after eating and is relieved by rest. What is most significant is that the afflicted person automatically stops all effort as soon as he is seized with his pain. Neither friend nor physician must tell him to rest. He will do it without being told. This behavioral reaction of the individual suffering from angina pectoris to his pain has been known for years. For the purposes of this paper, this will be considered the definition of angina pectoris.

The character of the pain associated with angina pectoris and with a coronary occlusion is usually the same. The features that commonly distinguish the two conditions are these: In angina the pain is of short duration; frequently it is less intense but not always so; and finally systemic effects are absent or transient.

The description of the acute episode of a coronary occlusion as given in three textbooks<sup>7, 8, 9</sup> consulted emphasizes the picture of collapse, which is frequently present early in this condition. The inference which is easily drawn by the reader from these descriptions is that the patient probably reacts to the pain of an acute coronary occlusion as he would to an anginal attack. Namely, he desires to rest. However, it must be remembered that when the patient is first seen by a physician, several hours may have

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elapsed from the time of onset of symptoms. By this time the patient usually is in the state of collapse described. However, when the patient's symptoms are considered in relation to time, the majority of patients seized with an occlusion will show varying periods of activity immediately following the onset of their pain. This period of activity may then be followed by the desire or necessity to rest. Therefore, the state in which the patient is first seen does not necessarily represent the state he may have been in immediately following the onset of his symptoms.

The conclusions presented in this paper are drawn from observations made on 28 successive patients suffering from acute myocardial infarctions. All of these patients were observed personally. These attacks were initial ones in so far as it could be determined from all available evidence. This point is emphasized. Frequently patients, who have suffered from one occlusion, suffer further episodes of pain. These episodes may appear to be further occlusions. However, it is often difficult to establish by the usual clinical and laboratory means exactly what has happened to the myocardium. For this reason episodes of a coronary type of pain occurring in those individuals known to have had a previous occlusion were not included. Therefore, the conclusions presented here do not necessarily apply to this class of patients.

In this group, 22 patients were male and six female. Sixteen survived and 12 died. Of the 12 who died, 10 came to autopsy, and the diagnosis was confirmed post mortem. The usual clinical and electrocardiographic criteria were followed in making the diagnosis, i.e. the presence of a characteristic pain and a clinical course accompanied by some or all of the following: Fever, elevation in white blood count, elevation in sedimentation rate, drop in blood pressure, presence of a gallop rhythm, or presence of a friction rub. Of the 16 patients who survived, 13 had classical changes in serial electrocardiograms to confirm without doubt the clinical diagnosis. Three cases were included in which there were significant changes demonstrated in serial electrocardiograms, but not classical changes. However, other features of the illness in these three individuals made the diagnosis appear so definite that all observers who saw the patients were in agreement.

The procedure followed in this investigation was to question all patients in detail as to symptoms suggestive of angina pectoris prior to the onset of their present illness. In addition, they were questioned as to the nature of their acute pain, its radiation, and its duration. They were also encouraged to recall exactly what they were doing when the pain first occurred, and what they immediately did thereafter. The usual routine history and physical examination were done as well.

It was of interest to note how vividly most of the patients could recall with accuracy just what they did. There were a few patients who at first did not understand what was wanted of them. These individuals had not considered their activity following the onset of their pain as anything that would be of interest to the examiner. If a leading question had to be asked,

it was stated in a manner such as this: "Did you remain sitting in your chair?" or if the patient was in bed at the time of the attack: "Did you remain in bed?" It was felt that if suggestion had to play a part in eliciting information, it would be better to ask the question opposite to the anticipated answer. A few patients were so acutely ill at the time of admission that detailed questioning was deferred until later. This was usually true of those patients admitted with acute pulmonary edema, which had been precipitated by a coronary occlusion.

Of the 28 patients interviewed, 18 stated that they immediately walked about with the definite feeling that walking or movement might provide them with relief. An additional four patients gave a history of walking, but they had no conception of why they did it. As far as these individuals were concerned, they just walked. Another five patients felt that their activity was motivated by the necessity to vomit, urinate, or defecate, and that the walking was necessary to get to the bathroom where these things could be most easily done. Only one patient showed no activity of significance. The duration of the activity was as follows:

Eleven patients showed a period of activity from five to 15 minutes; five patients showed a period of activity from 15 minutes to one hour; four patients showed a period of activity from one to two hours; seven patients showed a period of activity from two to 15 hours.

Several patients experienced premonitory attacks of pain. On reviewing the exact nature of the pain, its duration, and its severity, it was difficult to distinguish the premonitory episode from the one which was considered to bring about the final occlusion of the vessel. However, some of the patients who had premonitory pains described them as less intense and shorter in duration than the final attack of pain. The significant feature in regard to the premonitory type of pain was that the patient responded by walking if he had been at rest or usually continued his work if the attack came on while he was working.

As far as could be determined from the patients in this series, activity was an immediate response and was not engaged in after a trial period of rest had failed to relieve the pain. This point was best exemplified by those patients who previously suffered from angina pectoris. These individuals stated that they had no thought of resting as they did with their anginal attacks but immediately began some form of effort.

Five cases will be presented, which illustrate the variety of responses obtained in the group as a whole.

#### CASE REPORTS

*Case 1.* R. L., a 75 year old white, married male, was in fair health until the morning of April 4, 1947, when he was awakened from a sound sleep by a severe pressing substernal pain. He immediately sat up in bed and rubbed his precordium violently. In a few moments, he got out of bed and walked to the bathroom where he attempted to have a bowel movement and vomit. He then walked back to his bed-

room, called his wife, and went to bed. He progressed rapidly into a state of peripheral vascular collapse and was brought into the hospital about two hours later in very poor condition. However, he was able to give a good account of his symptoms. His past history was essentially negative, except that during the past six months he had suffered from a vague epigastric distress, which conceivably may have been an anginal type of pain. It was not possible to go into detail on this point because of the patient's condition. The physical examination at the time of admission revealed a thin, acutely ill, white, elderly male, lying quietly in bed breathing with a mild Cheyne-Stokes respiratory rhythm. The temperature was 101°, pulse 140, respirations 20, and blood pressure 55/0. The skin was pale, cool, and moist with moderate cyanosis of the lips and extremities. The lungs showed fine moist râles at both bases. The heart was not enlarged to percussion, and M<sub>1</sub> was absent. At times a gallop rhythm was audible over the precordium. The only laboratory examination done was an electrocardiogram, which showed elevation of ST<sub>1</sub> and ST<sub>2</sub>. The QRS complexes were slurred and notched with an intraventricular conduction defect. The patient died 16 hours after admission. At autopsy a massive anterior myocardial infarction was discovered with atherosclerosis of the left coronary artery with thrombus formation present in the first third of the left coronary artery.

*Case 2.* S. W., a 78 year old widow, had been in good health until the morning of Sunday, April 13, 1947, when she was seized with a severe pressing pain in the back between both scapulae. She was riding on a bus at the time on her way to church. She continued on her way, and the pain abated. Twenty minutes later while sitting in the church, she was seized with a severe constricting pain beneath the sternum radiating through to the back. She thought that she might feel better if she could get up and walk. She left the service and walked out to the vestibule where she paced about for ten minutes but had no relief from her distress. A taxi was summoned, which took her home, and from there she was sent into the hospital. Her past history was negative, except for possible hypertension. She had been in extremely good health all her life. Physical examination at the time of admission showed a well developed, elderly, white female lying quietly in bed complaining of severe precordial distress. The temperature was 99°, pulse 100, respirations 20, and blood pressure 150/80. The skin was warm and dry without cyanosis. The lungs were clear to percussion with rhonchi audible throughout both lung fields and moist râles at both bases. The heart borders could not be percussed accurately. The heart sounds were of poor quality and easily obscured by the breath sounds.

No electrocardiographic or laboratory studies were made before death. The patient gradually went into peripheral shock and died five hours after admission. Autopsy showed occlusion of the left coronary artery with rupture of the intraventricular septum.

*Case 3.* F. P., a 59 year old mechanical engineer, was in good health until 8:30 on the morning of March 30, 1947, when he was seized with a sense of fullness in the epigastrium. It felt as though there was some gas in the stomach which could not be brought up by belching. This fullness was soon merged with a squeezing and pressing sensation in the precordium, which radiated down both arms. Immediately after the onset of pain, he got up and walked up and down the living room for about three hours without once sitting down. He felt no better after this time and a physician was summoned who came and found him still pacing up and down the floor. A diagnosis of a coronary occlusion was immediately made and the patient sent into the hospital. His past history revealed that he had been feeling tired for about one year, and that he had occasional episodes of indigestion and constipation. However, these bore no relationship to effort or to meals, and no clear conception could be gained as to their cause. He had been in the hospital six weeks prior to the present admission at which time sigmoidoscopy, barium enema, and an electrocardiogram were all normal.

Physical examination showed a well developed and well nourished, slightly obese, white male with a florid, healthy appearance. His temperature was 98.6°, pulse 84, respirations 17, and blood pressure 130/80. The skin was warm, dry, and without cyanosis. The lungs were clear to percussion and auscultation. The heart was enlarged slightly to the left. The sounds were of fair quality.

The laboratory findings on admission showed a white blood count of 7,600 and a sedimentation rate of 10 mm./hour.

An electrocardiogram taken on March 31, 1947, showed all ST segments to be isoelectric.  $T_1$  was isoelectric and  $T_4$  was deeply inverted and cove shaped. The electrocardiogram taken six weeks previously showed T-waves upright in all leads. Another electrocardiogram taken on April 11, 1947, showed  $T_1$  and  $T_4$  inverted with  $T_4$  more deeply negative. A final electrocardiogram taken on May 2, 1947, showed  $T_1$  upright and  $T_4$  less negative.

While in the hospital, the patient ran a low grade fever between 100° and 101° for the first five days, and then it returned to normal. His sedimentation rate became elevated for a time, and he displayed a gallop rhythm for a few days shortly after admission. Except for a few recurrent episodes of precordial distress coming on after meals, he did well and was discharged to his home on the thirty-eighth hospital day.

*Case 4.* J. C., a 55 year old common laborer, had been in good health until the first week of July, 1947, when he began to notice the frequent occurrence of substernal pressure following exercise, which was relieved by rest. Whenever this pain occurred, he instinctively stopped all effort. About three o'clock on the afternoon of August 3, 1947, while sitting on a park bench, he was seized with a sudden and severe sense of substernal oppression and squeezing. The pain radiated down his left arm. He immediately arose from the bench and walked about for a few minutes. Then he walked over to a nearby lunchroom and bought a bottle of ginger ale with the idea that it might help to bring up gas, which in turn might relieve his discomfort. This did not happen, however, so he went back to the park and sat down on the bench for a few minutes and then again got up and walked about until the pain gradually subsided in intensity. He then walked a mile to the emergency department of this hospital where he was immediately put to bed and given morphine to relieve his residual discomfort. His past history revealed that he had a hypertension of over 200 for several years, and that he had been treated for syphilis.

Physical examination showed a well developed, ruddy faced, white male, who did not appear particularly ill. His temperature was 100.6°, respirations 18, pulse 80, and blood pressure 174/106. The heart was not enlarged, and the sounds were of fair quality without murmurs.

The laboratory findings showed a white count of 9,600 on admission and a sedimentation rate of 37 mm./hour. An electrocardiogram taken on August 4, 1947, showed slight slurring of QRS in all leads with  $T_1$  inverted,  $T_2$  isoelectric. There was an absent  $R_4$ ;  $ST_4$  was slightly elevated with a deeply negative  $T_4$ . Another electrocardiogram taken on August 9, 1947, showed  $ST_1$  slightly elevated with coving of  $T_1$ . There was moderate elevation of  $ST_4$  with a diphasic  $T_4$ . A final electrocardiogram taken on August 25, 1947, showed  $T_1$  deeply inverted with  $ST_1$  isoelectric with a  $T_4$  so deeply inverted that the apex could not be recorded on the paper.

While the patient was in the hospital, he had a low grade fever for five days. He had a definite gallop rhythm during his first week in the hospital. He was discharged improved on the thirty-fourth hospital day.

*Case 5.* W. U., A 64 year old retired business man, was seized with a pressing epigastric non-radiating pain about 11 o'clock on the evening of August 3, 1947. He was sitting in a chair reading at the time. A few moments after the onset of the pain, he arose from his chair and walked to the kitchen, where he took a shot of whiskey with the hope that it might relieve his discomfort. However, it grew worse, and he

walked upstairs to his bedroom. After a few minutes in bed, he walked to the bathroom and vomited. He still was not relieved from his pain, so he walked up and down his upstairs hallway for about one-half hour, hoping that the pain would subside. Finally his wife suggested that he lie down, and a physician was called who made the diagnosis of a coronary occlusion and gave him morphine for relief. He was sent into the hospital by ambulance the following morning. His past history was significant in that he had been a known hypertensive for 15 years, and that five years prior to this admission he developed typical angina pectoris. His anginal episodes had been characterized by the presence of a precordial pressing sensation with radiation of pain down the left arm. The episodes came on after effort and ceased with rest. The angina lasted for about one year and gradually disappeared so that the patient was completely free of angina on ordinary effort for about three and one-half years prior to this episode. The pain associated with his occlusion differed in location and nature from that which he experienced with his angina.

The physical examination at the time of admission was not remarkable. The patient did not appear acutely ill. The temperature was 99°, the pulse 110, the blood pressure 150/120. The lungs were clear. The heart was enlarged to the left. The first heart sound was of fair quality. The rhythm was regular, with the exception of occasional premature contractions.

The laboratory findings showed a white count of 19,100 on admission, and the sedimentation rate was 15 mm./hour. An electrocardiogram taken on August 4, 1947 showed slight elevation of ST<sub>1</sub> with inversion of T<sub>1</sub>. R<sub>1</sub> was absent. ST<sub>4</sub> was elevated, and T<sub>4</sub> was inverted. An electrocardiogram taken on September 10, 1947, showed a characteristic "healing" stage of an anterior myocardial infarction.

While the patient was in the hospital, his temperature rose to 102° and remained there for six days and returned to normal gradually during the following two days. The sedimentation rate became elevated to 40 mm./hour. He also presented a gallop rhythm for several days following admission. About one month after admission while appearing to get along well in every way, he developed acute pulmonary edema and was digitalized. He had no further difficulties and was discharged from the hospital seven weeks after admission. He died with acute pulmonary edema while at home one month later. An autopsy was not obtained.

The activity shown by the following patient was so minimal that it was impossible to interpret it as anything other than the type of response anticipated in angina pectoris.

*Case 6.* S. M., a 55 year old white plumber, was in fair health until August, 1947, when he noted the occasional occurrence of a full feeling in the epigastrium, which he thought was indigestion. This fullness came on after effort and was relieved by rest. At four o'clock on the morning of September 8, 1947, he was awakened from a sound sleep by the same type of pain, which he had had previously on effort. This time the pain was more severe and gradually radiated over the precordial area and down both arms. Soon after its occurrence, he sat up in bed and rocked backwards and forwards slightly. He did not leave his bed nor did he engage in any more activity other than that described. He was seen by his physician about four hours later. He was given nitroglycerine sublingually without relief. He was then given morphine and sent into the hospital. He had no vomiting, dyspnea, cyanosis, or diaphoresis. His past history included a subtotal thyroidectomy at the age of 15, a cholecystectomy at the age of 48, and a radical right mastectomy for carcinoma of the breast at the age of 50.

The physical examination showed a well developed, muscular, middle-aged, white male, who appeared in mild distress. His temperature was 98°, pulse 100, respirations 17, and blood pressure 180/130. The lungs were clear to percussion and auscultation. The heart was enlarged to the left, and an apical grade II systolic murmur was audible. The heart sounds were of fair quality.



The laboratory findings on admission showed a white count of 16,700 and a sedimentation rate of 33 mm./hour. An electrocardiogram taken on September 9, 1947, showed gross elevation of ST<sub>1</sub> and ST<sub>2</sub> with T<sub>2</sub> and T<sub>3</sub> inverted. The QRS complexes were grossly slurred and notched. R<sub>1</sub> was absent.

While the patient was in the hospital, he developed a temperature of 104° the day following admission, and it ranged between 102° and 104° for five days, when it gradually returned to a normal level during the next three days. A pericardial friction rub was audible for about 12 hours on the second hospital day. He then developed a definite gallop rhythm, which was present for about five days. He remained in the hospital for three weeks and was sent home to continue bed rest. He died two days later. No autopsy was done.

In the case that follows the acute episode of pain was mild. When I saw this patient I was doubtful as to the significance of the incident when I considered only the duration of the pain and its severity. The physical findings were meager. My first impression was to refer him for further ambulatory study. However, consideration of the behavioral response to the pain and especially the consideration of the fact that it differed from the previous response to a similar pain made me conclude that the man probably had a coronary occlusion, and I admitted him for further study. Therefore in this particular patient I felt that the knowledge of the behavioral response was the additional piece of evidence that allowed me to treat the man as he should have been treated. Otherwise, I am sure that I would have allowed him to remain ambulatory until further developments forced the true state of affairs to my attention.

*Case 7.* W. W., a 64 year old unemployed factory worker, had been in fair health until the middle of July, 1947, when he noted the frequent onset of a heavy pressing pain in the substernal and epigastric area after eating and after exercise. This pain would disappear after rest. On the evening of August 22, 1947, he felt the same discomfort, but rather than resting he felt like walking about to relieve his pain. He walked about for two hours until the pain gradually subsided. He came into the emergency department of this hospital the following morning to find out what could be done for him. He felt that the pain had not been any more severe than on previous occasions, but for some reason he was definitely more concerned about it than he had been about his anginal attacks. His only other complaint was that he had been slightly more dyspneic following the attack of pain on the previous night than he had been previously. His past history was otherwise non-contributory.

Physical examination showed a thin, lanky white male who did not appear acutely or chronically ill. His temperature was 98.6°, pulse 104, respirations 20 and blood pressure 130/80. The lungs were clear to percussion, but there were a few fine râles at both bases. The heart was not enlarged, and the sounds were of good quality without murmurs.

The laboratory studies on admission revealed a white blood count of 37,900, and a sedimentation rate of 34 mm./hour. An electrocardiogram taken the day of admission showed slight sagging of ST<sub>1</sub> and ST<sub>2</sub> with moderate sagging of ST<sub>4</sub>. T was upright in all leads. There was an early intraventricular conduction defect in all leads. Another electrocardiogram taken on August 26, 1947, showed all QRS complexes to be of lower voltage when compared with the previous tracing. T<sub>1</sub> was isoelectric and T<sub>2</sub> was of low voltage. A final electrocardiogram taken on September 3, 1947, showed all ST segments to be isoelectric and T<sub>1</sub> and T<sub>4</sub> inverted with T<sub>2</sub> isoelectric.

While the patient was in the hospital, he ran a temperature varying between 100° and 100.8° for three days. His sedimentation rate remained elevated for three weeks and gradually returned to normal. Toward the end of the fourth week he experienced some further precordial pain on effort. He was discharged improved after five weeks in the hospital.

## DISCUSSION

In summary, I believe that a distinction can be made between the pain of angina pectoris and that associated with a coronary occlusion on the basis of the inherent behavioral response of the individual to his pain. The patient with angina pectoris characteristically has his pain on effort, and the instinctive response to this pain is cessation of all effort and motion. On the other hand, the patient seized with a coronary occlusion is frequently at rest although he may be at work, and his instinctive response to this pain is effort lasting from five minutes to several hours. Effort in this series of patients was manifested as walking.

The frequency of this response can probably be visualized best by a consideration of the normal distribution curve. This curve applies to the frequency of occurrence of most biological phenomena. There will undoubtedly be occasional cases such as the one described here that do not present this behavioral response, as there are undoubtedly cases of coronary occlusion that do not have pain. However, the greatest number of patients should show a period of activity immediately following their acute episode of pain ranging from 10 minutes to four hours. Activity less than or more than this should occur with decreasing frequency.

An understanding of the usual behavioral response of a patient with a coronary occlusion is also helpful in distinguishing a genuine occlusion from a simulated occlusion. Those patients whose symptoms are motivated either by obvious malingering or on a more subtle neurotic basis usually convey the idea to the examiner that their pain causes complete and immediate cessation of all activity. The neurotic or malingerer will not show activity following the onset of his pain.

It is my belief that all patients who appear to have a definite coronary type of pain and respond to their pain with some evidence of effort should be considered as potential coronary occlusions. If this distinction is followed, there will be some cases admitted for study in which the diagnosis will be difficult to establish electrocardiographically. This has occurred in two patients during the period of this study. The possibilities that have to be considered are that these two individuals either did not have an occlusion, or if they did have one, the myocardial damage was so minimal that no changes of significance could be discovered. Finally, they may not have had heart disease, and their symptoms may have been due to some other undiscovered cause. Intensive follow-up studies on this type of patient should be helpful in further evaluating the reliability of this factor.

## SUMMARY

Twenty-eight cases of coronary occlusion with myocardial infarction are presented, of which 27 showed an immediate response to their pain of effort lasting from five minutes to 15 hours. The general thesis is advanced that

an additional distinction can be made between the pain of angina pectoris and that associated with a coronary occlusion on the basis of the behavioral response of the patient to his pain.

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## AN HISTORICAL REVIEW OF THE PHYSICAL EXAMINATION OF THE CHEST \*

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THERE is no part of medicine that offers so great a challenge to the medical mind as diagnosis. Early diagnosis detects disease when the least harm has been done to the patient and makes treatment more simple and cure more probable. Then too, if the disease is infectious, it permits early application of public health measures for the protection of others.

Any method of examination which adds to the earliness or the certainty of diagnosis is a valuable contribution to the welfare of man.

For a long time it was thought that disease was a general disorder involving the whole organism. However, in 1761 Morgagni<sup>1</sup> published his book on pathological anatomy, and Auenbrugger<sup>2</sup> devised percussion for the examination of the heart and lungs. It was thus shown both pathologically and clinically that some illnesses had their seat in organs.

It is nearly two centuries since the physical examination of organs within the chest was made possible by Auenbrugger through percussion, and a century and a quarter since their examination by auscultation was made possible by Laennec and the stethoscope.

There is no record of percussion having been used in the examination of the organs of the chest prior to 1754, when Leopold Auenbrugger of Vienna struck the normal chest of a patient with the tips of his fingers and noted a resonant sound. However, Skoda states that the abdomen had been previously percussed to determine the presence of gas in the bowel. Auenbrugger found that a stroke over the heart gave a dull sound and over a normal lung a resonant sound. However, he also noted that when the lungs were diseased a different sound was elicited. He found, on post mortem, that those areas of the lungs over which he had obtained a dull note on percussion contained less air than normal and that those which showed hyperresonance contained more air than normal. After seven years of percussion and noting sounds and comparing clinical and postmortem findings, Auenbrugger in 1761 published *Inventum Novum*, a small book of 95 pages which contained the results of his clinical observations, describing resonant, dull and tympanitic notes—the conditions responsible for all of which he had proved post mortem.

The following quotation from *Inventum Novum* is taken from a translation published in Castiglioni's History of Medicine:<sup>3</sup>

"I. The thorax of a healthy person sounds, when struck.

"II. The sound thus elicited from the healthy chest resembles the muffled sound of a drum covered with a thick woolen cloth or other envelope. . . .

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"XII. If a sonorous part of the chest struck with the same intensity yields a sound deeper than natural, that part is diseased where the note is deeper.

"XIII. If a sonorous part of the chest struck with the same intensity yields a sound duller than natural, disease exists in that part. . . . I have opened the bodies of many dead from this disease (consumption) and I have always found the lungs firmly bound to the pleura, and the lobes on that side where the obscure sound has existed callous, indurated, and more or less purulent."

Auenbrugger is supposed to have obtained the idea of percussion from seeing his father, who was an innkeeper, tap on wine barrels to estimate their contents. However, the fact that he lived in Vienna at the time of Gluck and Haydn and was himself a devotee of music might also have had much to do with it. He not only was a distinguished physician but also entered into the cultural life of Vienna. He was a Styrian, born in Gratz. In 1784 the Emperor gave him a patent of nobility. Auenbrugger wrote an opera, *The Chimney Sweep*, which would indicate that he had a high appreciation of musical tones.

Van Swieten was head of Viennese medicine and was greatly admired by Auenbrugger. He and his successors, de Haen and Stoll, taught the necessity of studying the patient. DeHaen introduced the thermometer into Viennese medical circles. However, not one of these clinicians saw that Auenbrugger had opened new vistas in medicine. In their writings on diseases of the chest not one of them recommended percussion, but Stoll mentioned it in his Aphorisms. This caused Auenbrugger great disappointment, but he said he expected such treatment of his discovery and did not let it dissuade him from continuing his observations.

Although percussion had within it the possibility of furnishing a better understanding of chest diseases, physicians were slow to adopt it, and Auenbrugger died without its being accepted.

About 50 years later Corvisart, finding little progress in France, turned to Viennese medicine, which was in the ascendancy at the time. He learned of percussion through his translation of Stoll's Aphorisms. Percussion had not come to his attention in Paris. In fact, it was all but forgotten. But Corvisart on learning of it was immediately impressed with its possibilities. He used it daily in practice and did everything in his power to induce others to use it. In 1808 Corvisart<sup>5</sup> brought out an elaborate translation of *Inventum Novum*, expanding it from its original modest 95 pages to 440 pages.

On hearing that Corvisart diagnosed diseases of the chest by examining that part of the body direct, Napoleon, who was ill, said: "Send him to me." Corvisart came and tapped Napoleon's chest with his fingers and made a diagnosis. This so impressed Napoleon that he appointed him his personal physician. It was from this vantage point that he was able to revive percussion and establish it for all time, but not without great opposition on the part of his confreres.

As professor of practical medicine in the College of France, he taught that diagnosis depends on accurate observation.

Corvisart not only revived the almost forgotten percussion but stimulated his distinguished pupil, Laennec, to observe and examine. Laennec was a student of acoustics and also a musician (player of the flute), therefore it was not unnatural that his attention should be turned to percussion and auscultation. Laennec not only felt the pulse and percussed the heart, but he listened to the heart sounds with his ear to the chest. This was often disagreeable—sometimes to the physician on account of the lack of cleanliness; sometimes to the patient on account of modesty. It is said that 15 days before he discovered the stethoscope he read a paper on immediate auscultation before the Societe de L'Ecole, which not only shows his great interest in auscultation before he discovered the stethoscope but also indicates the suddenness of his discovery. This was in February 1815. It is said to have been the first paper recorded on *immediate* auscultation, and yet *mediate* auscultation was just about to be born.

The story of the discovery of *mediate* auscultation is the following. Laennec had a very obese woman patient whose heart sounds he could not hear clearly. The patient was not only obese but modest and he could not bring his ear in contact with the area of the heart sounds. He saw some boys playing with timbers lying in the courtyard of the Louvre. One of the youngsters tapped on the end of a long beam and another put his ear to the other end and could hear the transmitted sound. This gave Laennec an idea. On arriving in the presence of his patient he made a roll of paper, put one end over the site of the cardiac impulse and with his ear to the other end heard the sounds with unusual distinctness. He then listened to the lungs and heard the respiratory sounds with clearness and satisfaction. In this manner the stethoscope was discovered and Laennec was able to report the first description of the sounds heard on respiration.

For four years Laennec worked, observing patients and, like Auenbrugger, when possible compared his findings with postmortem results. In 1819 he published his observations on the use of the stethoscope in the study of diseases of the heart and lungs. In this he described the respiratory sounds as he heard them in normal chests and in the various diseases of the lungs.

Laennec's book <sup>6</sup> *De L'Auscultation Médiante* (Paris 1819), like *Inventum Novum* of Auenbrugger, was given a poor reception. Many saw in the stethoscope no advantages over previous methods of examination and feared that mechanical instruments would ruin clinical observation. What would they think of today's armamentarium?

Those who refused to see value in it were those especially who had not seen its demonstration, but those who witnessed Laennec's demonstrations were convinced. The numbers of his pupils were many, and the French school prospered. Skoda of Vienna and Piorry of Paris both adopted and enthusiastically demonstrated percussion and auscultation. Piorry <sup>7, 8</sup> was

the first to use the pleximeter. He also taught the value of the resistance felt by the percussing fingers, although Corvisart had the honor of being the first to note this phenomenon.

Physical diagnosis based on percussion and auscultation was gradually established. It was fortunate to have as its sponsors, Auenbrugger, Laennec, Corvisart, Piorry and Skoda.<sup>9</sup> In two of these the spark of originality had lighted the way to a newer clinical conception, and the others were far-sighted enough to recognize the value of these discoveries to medicine and the world.

Medicine had made great advances in the 50 years following the discovery of percussion and should have been better prepared to receive the work of Laennec, yet it was received only half-heartedly. But it was saved by the enthusiasm of a few great teachers who came in contact with Laennec and others who followed him.

Many physicians from different parts of the world came to Paris to study with Corvisart and Laennec. This made Laennec's work too arduous for his frail body. He was suffering from tuberculosis and was compelled for a time to give up his teaching and to repair to his old home in Brittany. His enthusiasm, however, compelled him to return to his work sooner than he should have done. He observed, he taught, he wrote; and, in 1826, just after finishing a second book<sup>10</sup> Laennec fell seriously ill and soon thereafter died.

Laennec stated: "Immediate auscultation, however, should not cause us to forget the method of Auenbrugger; on the contrary, it confers on it an importance altogether new, and extends its use to many diseases in which percussion alone affords no indication." He was exceedingly optimistic about the readiness with which physicians could master auscultation. He stated: "It is, however, sufficient to have observed a disease two or three times to know how to recognize it with certainty."

Laennec stated that immediate auscultation was tried by Hippocrates but there was no evidence that from the time of the Father of Medicine to his time anyone had repeated the experiment.

Laennec paid little attention to expiration. He was particularly engrossed with the idea that he was able to hear the air pass down through the bronchi and into the alveoli. Starting with the trachea, he spoke of tracheal breathing; he followed, in his mind, the air through the bronchi and called that *bronchial breathing*. Then he assumed that the air cells were opening and called that *vesicular breathing*. Combinations of the latter he called *broncho-vesicular*.

He assumed that the murmur which he heard originated in the pulmonary tissues and bronchi immediately under the stethoscope. This is partly true. The pulmonary tissues do have a part but not the only part in the production of the respiratory murmur, and also a part but not the only part in its transmission to the ear, as may be inferred from the murmur produced and transmitted over the abdominal muscles in abdominal breathing.

He described the finding of *bronchial breathing*, normally, over the large bronchi near their bifurcation; and *vesicular*, in the axilla near the surface of the lungs at the end of the bronchi, particularly, where they passed into air cells. Bronchial breathing heard elsewhere he considered pathological; likewise the failure to find vesicular breathing where it was expected to be. He reasoned that when the air cells are filled with exudative material the only sound heard must be that of the bronchi, hence pneumonia and tuberculous consolidation cause bronchial breathing. He noted the increased intensity of the spoken voice, *bronchophony* in case of infiltration of the lung; and the transmission of distinct syllables, *pectoriloquy*, in case of cavity. It must be remembered that many of his patients suffered from far advanced tuberculosis, with cavitation. The recognition of early lesions is a recent accomplishment.

Laennec also gave us the classification of râles which has come down to the present with little alteration: "(1) the moist crepitant râle, or *crepitation*; (2) the mucous or *gurgling* râle; (3) the dry sonorous râle, or *snoring*; (4) the dry sibilant râle, or *whistling*; and (5) the dry crackling râle with large bubbles, or *crackling*."

In 1834, Beau<sup>11</sup> suggested that the air passing through the glottis was the cause of the respiratory murmur which was modified as it pressed against the walls of the trachea and bronchi and entered the alveoli. He seems to have accepted Laennec's description of the sounds, differing only as to their origin.

Laennec's description of the respiratory sounds and Beau's suggestion as to their origin have been accepted, taught, and described in textbooks until the present time.

Discoveries which carry the mind into fields of thought alien to those prevailing at the time, if not accepted at once, may be lost. Percussion had no outstanding champion until Corvisart took it up 50 years after Auenbrugger had published his discovery. As Corvisart had been obliged to teach himself percussion, so Skoda of Vienna taught himself both percussion and auscultation; and in 1839 published a Treatise on Percussion and Auscultation—78 years after Auenbrugger had published his *Inventum Novum* and 20 years after Laennec's publication on stethoscopic examination of the heart and lungs. Skoda's understanding of auscultation and percussion and the acceptance of it by his pupils may be envisaged by the fact that his book went through six editions between 1839 and 1864. Nevertheless, in spite of the fact that percussion and auscultation received the benefits of the prestige of Corvisart, Piorry, and Skoda, they were slow in receiving general recognition.

But once accepted, the remaining portion of the nineteenth century became distinctly the era of physical diagnosis in diseases of the chest, based on percussion and auscultation. Physicians improved their practice by comparing their findings with the postmortem results furnished by the rapidly



developing school of pathologists, beginning with Morgagni and followed by Rokitansky and Virchow in the nineteenth century.

In case of the examination of the heart and lungs, in the nineteenth century, inspection gave little direct information to the physician. The use of inspection was confined to the general appearance of the patient and to abnormalities in form and movement. Palpation was confined largely to eliciting the heart-beat, the thrill of murmurs, vocal fremitus, the thrill of large bubbling râles in lung cavities, and large rhonchi, and enlarged glands. Laennec noted that under certain conditions these large râles produce sounds resembling "a drum or a carriage rumbling over a pavement . . . accompanied by a vibration very sensible to the hand and indicative of its proximity."

It was not until after the beginning of the twentieth century that the clinician could use inspection and palpation as major methods of diagnosis of the organs within the chest. By this time the roentgen-ray had been discovered which, while being our greatest single method of examining the chest, has all but proved the fears of those who saw danger to methods of observation in the mechanical wooden stethoscope used by Laennec. However, it must be remembered that mechanical devices can not displace the senses in securing diagnostic data. The patient is an anatomical, physiological and emotional being, in whom departures from normal can be only partly detected by laboratory technics. The mind is necessary to interpret laboratory results and to fit them to the patient's reactions. The more accurate the physical examination made by the clinician the more evident will be the necessity of controlling roentgen-ray findings by data obtained by the eye, the ear, and touch.

When I studied in European clinics in 1894, the wooden monaural stethoscope was in general use, and not infrequently the ear to the chest was used. I do not recall a single European clinician who used a binaural instrument. Percussion was interpreted largely by sound instead of resistance. Different teachers had their own favorite pleximeters, some of wood, others of ivory, and still others of metal. Most, however, appreciated the fact that the best pleximeter was the finger, the differences in perception being of more value than sound. Likewise all kinds of percussion hammers were used—large and small—with little or much rubber on the striking surface. It was taught that light percussion would detect densities near the surface of the chest wall but that heavy blows were necessary for infiltrations deep in the chest. I well remember a professor in Berlin who used finger-finger percussion and could percuss for an entire amphitheater of students, the sound being so loud that it could be heard generally. Such blows throw the entire chest and all structures in the direction of the blow into vibration, cause confusion in interpretation, and may completely obscure the dullness caused by slight pathological changes.

On my first trip to Europe I was instructed in the usual textbook teachings on physical examination, the same as in Cincinnati. However, these were the smallest part of what I learned. I learned something of what the

great men in medicine were doing and thinking, and how they were interpreting their findings in terms of clinical disease. Even with their limited measures they did not hesitate to face the pathologist in case of post mortem.

I heard Senator lecture for one hour on what could be determined of a patient's past illnesses, present condition and future possibilities by inspection. I was more than impressed; I was astounded. How could he see so much, was the question which perplexed me.

In 1895, soon after my return from Europe, I was forced to leave Cincinnati and go to California on account of my wife's illness; and again to leave Los Angeles, our only city in Southern California at that time, with its 60,000 inhabitants, and go to Monrovia, a town of 600 people, in the foothills of the Sierra Madre mountains, because it was a more favorable climate. I had no special knowledge of tuberculosis, but my wife and most of my patients were suffering from it, so I was forced to teach myself. I was particularly anxious to know how to examine chests. I read my textbooks with great care. I tried to apply what I read to the chests that I had to examine. In auscultation I had great difficulty. I could not find the 5-3 or 3-2 ratio of inspiration to expiration given in the books. I found the sounds more nearly equal. I thought I must be wrong. It must be due to my inability to examine, but try as I would I could not make my findings correspond with textbook teaching. It took time for me to think the textbooks were inaccurate, but why should there not be error in textbooks? Everything is not discovered at one time.

One day I put my hand on a patient's back and struck a light blow on the front of the chest—so light that it was scarcely audible—and felt it perfectly through the chest. I then knew that percussion was more delicate than we had believed it to be and began to use a very light stroke—only a tap.

After proving to myself that teachings regarding the relative length of inspiration and expiration were wrong and after demonstrating that a light stroke could be felt clear through the chest, I one day placed my stethoscope over the biceps and noted a sound somewhat like the respiratory sound. I then came to the conclusion that part of the respiratory murmur might be muscular. I was strengthened in this opinion when I listened over the abdominal muscles and heard a murmur, weak but still similar to that often heard over the chest. My confusion was deepening. My own observations were directing me away from my textbooks and teachers.

Further study showed me that inspiration lasts during the entire inspiratory phase of respiration and expiration throughout the entire expiratory phase. It was just one more step to see that the respiratory sounds are caused by all factors in the respiratory mechanism that produce sound vibrations. The strange thing is that it took nearly fifty years after getting my first hint before I was able to take this step and fully satisfy myself that the respiratory murmur is composed of all factors belonging to the respiratory mechanism which are capable of producing sound vibrations.<sup>12, 13</sup>

It is evident to anyone conversant with the facts of physiology that the respiratory murmur can not be caused by the air rushing through the larynx and dilating the bronchi and air cells, because there is no rushing of air after it enters the trachea. The tidal air which amounts to some 500 to 700 c.c., on entering the air passages, is met by the residual air which nullifies its force. Thereafter the air enters the small bronchi and air cells by diffusion.

If the respiratory murmur is not caused by the action of the air column upon the bronchi and air cells, what would be a satisfactory explanation for the sounds heard in the different lung areas? I suggest that the respiratory murmur is caused by sound vibrations originating in all portions of the respiratory mechanism, and that they vary in quality according to the degree to which the sounds originate in air-containing and non-air-containing tissues.

Non-air-containing tissues are dominant in the upper portions of the lung in the region of the bronchi near the hilum anteriorly and in the interscapular space posteriorly. Here large bronchial and vascular trunks and a relatively small proportion of lung tissue are covered by a relatively large mass of musculature and the least elastic portion of the bony cage. Movement is restricted. In this area the murmur has been called *bronchial*. On the other hand, air-containing tissues are dominant in the production of sound in the outer and lower portions of the lungs. Here is a large proportion of pulmonary tissue and the bronchial and vascular trunks are relatively small and covered by a minimum of musculature and the most elastic portion of the bony cage. Here movement is relatively free. In this area the murmur has been called *vesicular*. In the presence of infiltrations the relative amount of non-air-containing tissues is increased, movement is restricted, and so the murmur takes on the so-called bronchial quality.

With this new conception of the respiratory murmur, auscultation becomes a method of studying the respiratory mechanism and the manner in which disease affects changes in respiratory movements and in the production and conduction of sound vibrations. It connects it intimately with inspection, palpation and percussion.

While studying physical examination I put to test my powers of inspection and palpation and tried many different types of percussion. I found that if we depend mostly on sound in percussion, the difference may be exaggerated by striking the chest with many different objects, such as a small rubber tube or a lead pencil. But these were only passing observations. I also outlined organs by palpatory percussion. However, I preferred to interpret percussion according to the sensation conveyed to the finger rather than sound. I learned to feel the effects of the percussion stroke and preferred the fingers for both hammer and pleximeter, using a very light stroke. It was just one more step to detect different densities by palpation, using no stroke at all; and this was soon proved.

At Monrovia I was isolated. I had no access to a library, but I could not get away from Senator's remarkable exhibition of inspection. So when

I began to teach myself to examine a chest, that remarkable lecture of Senator was always urging me to observe.

I could see the difference in movement of the chest wall and thought that differences over an infiltrated area as compared with a normal chest should also be felt. I palpated as well as percussed. After 14 years' trial I found that there was something felt over pathologic chests which was not noted over normal chests. Then one day I made an unexpected but important observation.

I was examining a patient who had marked infiltration at the right apex, with adherent pleura. Palpating over the first intercostal space I found a resistance greater than normal. I attributed it to the muscles. They seemed to be in spasm. I persisted and a few months later<sup>14, 15, 16, 17, 18, 19</sup> was able to demonstrate not only an increased density in the lung but a muscle spasm as well. I believed that I had observed the same spasm in inflammation of the lung as is found in appendicitis, inflammation of the gall-bladder and gastric ulcer.

I followed this lead carefully. I began to look for muscle tension in every patient whom I examined, and after a short time found that the lungs reflect in the muscles of the shoulder girdle—the sternocleidomastoideus, scaleni, levator anguli scapulae, acromial portion of the trapezius—and the crus and central tendon of the diaphragm. I found that all those muscles that are visible show spasm when the disease is active and degeneration when it is chronic or healed. I assumed that the same is true with the crus and central tendon of the diaphragm.

I also felt that it was not possible that the lessened motion on the side of the diseased lung in early cases could always be caused by the small infiltration present. I assigned it partly to the effect of spasm of the sternocleidomastoideus and scaleni above and the crus and central tendon of the diaphragm below interfering with the respiratory movement.

In my first observation I probably was feeling both the density of the underlying infiltrated pulmonary tissues and the spasm of the intercostal muscles caused by the underlying pleura. But the important fact was that I recognized increased tension and so persisted until I had found both the pulmonary and pleural reflexes and was able to differentiate them by the segments of the cord in which they were mediated, and had proved the ability to outline the heart and detect densities in the lungs by palpation.

I soon found that the muscles of the shoulder girdle and the crus and central tendon of the diaphragm receive their nerve supply from the mid-cervical segments of the spinal cord, particularly the third, fourth and fifth, and the pleura from the thoracic segments.

Sometimes, when active tuberculosis is present, one can see the muscles standing out in increased tension, but it is detected better by palpation. One can also see the lessened motion of the hemithorax which I have suggested might be partly caused by spasm of the sternocleidomastoideus and scaleni

above and the crus and central tendon of the diaphragm below. Aside from the spasm I found that the muscles, subcutaneous tissue and skin innervated by nerves from these same cervical segments show atrophy when the disease in the lung has become chronic or healed, and the skin and subcutaneous tissues overlying acute pleurisy atrophy when the pleural inflammation continues for any length of time.

The pleural motor reflex as shown in the intercostal muscles seems to be coextensive with the pleural inflammation. Both pleural motor and trophic reflexes are produced by the intercostal nerves which mediate in the same thoracic segments of the cord that receive the afferent impulses from the pleura.

The pleural trophic reflex, like the pulmonary trophic reflex, is of great importance diagnostically. It is not possible to differentiate the reflex pleural atrophy of the intercostal tissues from the degenerations which Coplin<sup>20</sup> has described as being caused by direct extension of the pleural inflammation to the intercostal structures; in fact, they are probably the same.

Inflammation in the lungs and pleura is easily differentiated reflexly because the pulmonary motor reflex is expressed in the muscles of the shoulder girdle (the accessory muscles of respiration) and the diaphragm; and the pleural motor reflex in the intercostal muscles. The atrophy caused by inflammation in the lung, aside from that in the muscles, involves the skin and subcutaneous tissues above the second rib anteriorly and the spine of the scapula posteriorly, while atrophy from pleural inflammation may involve the intercostal structures and subcutaneous tissues of the chest anywhere below the second rib anteriorly and the spine of the scapula posteriorly.

Our knowledge of the pulmonary and pleural reflexes offers aid in interpreting râles. While squeaks and wheezes are definitely signs of bronchial obstruction, the so-called moist râles are not so easily interpreted. They are not always caused by moisture in the air passages, nor are they always indicative of the presence of active tuberculosis when heard at the apex following a quick inspiration after exhalation and cough, as usually taught.

Râles which can not be differentiated from the so-called moist râles may be heard over the areas of pleural atrophy. Although at or near the apex they can not be differentiated from pulmonary râles, over the lower portion of the thorax their nature is more definite. Like the râles in tuberculosis, they are not always present. They are frequently found in patients with a history of previous pleurisy with effusion. I have known them to persist for years—in one case more than 40 years. The presence of the pleural trophic reflex without the pulmonary motor reflex is the key to the diagnosis. The roentgen-ray may show no pulmonary involvement, and there may be no history of recent pulmonary disease. The patient may complain of pain, for which a diagnosis of intercostal neuralgia is often made.

The discovery of the reflexes from the lung permitted me first to point out the important physiologic fact that while the lung receives its sympathetic

nerve supply from the upper five or six thoracic segments, the midcervical segments of the cord contain the centers in which the afferent nerves which course in the pulmonary sympathetic system mediate reflexes in the somatic structures—muscles, skin and subcutaneous tissues. In order to do this, stimuli must be conveyed from the lung to the upper thoracic segments, thence upward over intracentral paths to the midcervical segments, thus differing from other important viscera.

The pleural reflexes follow Sherrington's law<sup>21</sup> to the effect that each afferent impulse finds in the segment of the cord which it enters an efferent neuron with which it will mediate a reflex most readily; but to explain pulmonary reflexes it was necessary to suggest a modification of this law<sup>22</sup> as follows: *Each afferent impulse from the lung finds in that segment of the cord with which it is embryologically connected an efferent neuron with which it will unite most readily to produce reflex action.*

I also found that the afferent fibers in the vagus of the parasympathetic nervous system mediate with efferent neurons of the cranial nerves in case of the facial muscles, the Vth, VIIth and IXth in case of the tongue. The atrophy of the facial structures and tongue is best seen in chronic largely one-sided destructive pulmonary lesions and sometimes following thoracoplasty.

While pursuing the study of these reflexes, I one day (as previously stated) noted that I could detect the borders of the heart by palpation. It did not seem possible that an organ deep within the chest cavity could be felt. But by continuing my search I found that I could not only outline the heart by palpation but I could detect the difference between the density of normal lungs, infiltrated lungs, and distended lungs such as we find in asthma and emphysema. This could be detected by pressure so light that it barely indented the skin, so I called the method *Light Touch Palpation*.<sup>16, 23</sup> This gives a new method whereby one by palpation can outline the heart and differentiate various pathologic conditions in the lung and pleura by differences in density. Furthermore, it proves the validity of very gentle percussion.

During the nineteenth century physical diagnosis of organs within the chest was based only on percussion and auscultation. In the twentieth century, now that the reflexes from the lung and pleura have been described and the ability to palpate structures—both superficial and deep within the chest—has been discovered, physical examination becomes more accurate, and inspection and palpation assume major importance.

Physical examination of the organs within the chest has now been enriched, and the physician has at his command methods as accurate as his perception and interpretation of sight, hearing and touch can make them. Whether the disease is active or inactive can be determined by sight and touch. Furthermore, findings can be studied in connection with roentgenograms of the chest which afford a valuable method of recording the living pathology of these structures.

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# CHRONIC LEUKEMIA OF LONG DURATION: WITH A REPORT OF 31 CASES WITH A DURATION OF OVER FIVE YEARS \*

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NUMEROUS physicians have observed cases of leukemia of unusually long duration, but there is no published summary of many such cases. An analysis of unusual cases might add to knowledge of leukemia as a whole. Also if one could determine what factors lead to an unusually long duration, prognosis would be easier and therapy could be evaluated more readily. It therefore seems worthwhile to review the literature as it pertains to cases of leukemia of long duration and to select a group of such cases, from those seen by us, for analysis.

## DETERMINATION OF DURATION

The determination of duration presents a problem in a disease with an onset as insidious as that in leukemia. Most published reports have estimated duration from the onset of symptoms, but it is often difficult to date the beginning of such vague symptoms as weakness, easy fatigability, or general malaise. Minot and Isaacs<sup>25</sup> estimate that in 100 cases of chronic myelogenous leukemia an average of eight months passed between the onset of symptoms and the first visit to a physician, whereas in 72 cases of the chronic lymphatic type a nine months period elapsed. Widmann<sup>40</sup> considers that duration should be calculated from the date of diagnosis, which is known, rather than from the date of onset of symptoms.

The actual disease process may antedate the onset of symptoms by a considerable period. It is well known that chronic leukemia may be detected from routine examination of the blood prior to the onset of any symptoms.<sup>34</sup> Wintrobe and Hasenbush<sup>41</sup> estimate that two to five years—or longer—elapse between the actual time of onset of chronic myelogenous leukemia and the time when symptoms cause the patient to seek medical aid. In chronic lymphatic leukemia they<sup>41</sup> found that one and a half to two and a half years passed between the finding of signs of the disease (leukocytosis, glandular enlargement, or splenomegaly) and the development of symptoms of the disease. They believed lymphatic leukemia was discovered earlier in its course because of the associated lymph node enlargement.

Table 1 summarizes the average duration of cases of chronic leukemia as recorded in various reports. A notation is made as to what date was used

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TABLE I  
Average Duration of Cases of Chronic Leukemia in Years

Author	Duration Calculated from	Myelogenous			Lymphatic		
		No. Cases	Average Duration	Per cent >5 yrs.	No. Cases	Average Duration	Per cent >5 yrs.
Arendt and Gloor <sup>1</sup> Bethell <sup>2</sup>	Onset symptoms	39	4.3		22	4.2	
	Onset symptoms				52	0.33	
					(lymphoblastic)		
					70	2.6	
					(lymphosarc. cell)		
					68	4.85	
					(lymphocytic)		
Hoffman and Craver <sup>11</sup>	Onset symptoms	82	3.36				
	Beginning of treatment	82	2.62				
Jackson <sup>15</sup>	Onset symptoms			10			10
Lawrence et al. <sup>16, 16a</sup>	Onset symptoms	127	4.0+	30	100	4.5+	32*
Leavell <sup>17</sup>	Onset symptoms	87	3.2	20	49	3.6	20
Leucutia <sup>20</sup>	Onset symptoms	18	3.3		13	4.33	
	Beginning of treatment	18	2.1		13	2.5	
Minot <sup>24, 25</sup>	Onset symptoms	52	3.04		80	3.5	14
		(non-irrad.)					
		78	3.5	12	7	1.07	
		(irradiated)			(Aet. <30)		
Pascucci <sup>28</sup>	Onset symptoms	64	2.5	5	64	2.8	14.5
Reinhard <sup>31</sup>	Onset symptoms	21	3.64				
		(P <sup>32</sup> treated)					
Widmann <sup>40</sup>	Beginning of treatment	25	2.7		24	3.3	
Wintrobe and Hasenbush <sup>41</sup>	Date diagnosis	23	1.68		23	1.07	
	Onset symptoms	23	2.79		23	2.33	
Wintrobe <sup>42</sup>	Onset symptoms	259	3.28		152	3.29	

\* Many patients in both the lymphatic and myeloid groups are still alive—and it seems certain that the eventual figure for average duration will be five or more years.

by the authors in calculating duration wherever this information was ascertainable. Arendt and Gloor<sup>1</sup> described a small series of cases treated with arsenic and roentgen-ray. They did not give statistics but data calculated from their graphs show that their patients had a longer average duration than usual. This finding may have been related to the treatment given, or may simply be due to the small number of cases described. Bethell's review<sup>2</sup> of cases of chronic lymphogenous leukemia shows a longer duration of the lymphocytic type than is usually observed because he separated these from the lymphoblastic and lymphosarcoma cell types and because he obtained a good follow-up of most cases seen at the Simpson Memorial Unit of the University of Michigan. Sturgis<sup>35</sup> excluded cases of lymphosarcoma cell leukemia from cases of true chronic lymphatic leukemia when calculating duration. Lawrence et al.<sup>16a</sup> did not exclude these cases, yet they found also a relatively long duration and 22 of their patients are still living, so the average figure will be increased further. No significant difference was observed

between males and females with regard to duration of life in Hoffman and Craver's review.<sup>11</sup> Minot and Isaacs<sup>25</sup> noted that the age at which the disease occurred did not seem to affect the duration of chronic myelogenous leukemia but was a definite factor in the chronic lymphatic type where the disease apparently lasted a shorter time under the age of 40 years, and particularly under 30, than it did when it occurred between 40 and 60. Leavell's review<sup>17</sup> gave him a similar impression. Lawrence et al.<sup>16</sup> concluded that there were no remarkable differences in duration of the disease with various ages of onset in their series of 129 cases of chronic myelogenous leukemia but observed in the case of chronic lymphatic leukemia<sup>16a</sup> that the prognosis was better in the 30 to 40 age group. Widmann's report<sup>40</sup> deals with 49 patients who were treated and followed at the Philadelphia General Hospital. Patients with leukemia who were too ill to be treated, were not treated, or were not adequately followed, are excluded. The data by Win-trobe<sup>42</sup> represent cases previously reported by various writers and probably include cases listed elsewhere in table 1.

### PARTICULARLY LONG

Several reports are worth special mention because they describe cases of particularly long duration. These are summarized in table 2. Miller and Turner<sup>23</sup> emphasize the wide variation in life span seen especially in chronic lymphatic leukemia and state that an occasional patient may live 25 years with the disease. They may have had reference to McGavran's case.<sup>22</sup> Widmann<sup>40</sup> includes two patients with lymphogenous leukemia of 13 and 18 years' duration and two with the myelogenous type of 13 and 19 years' duration in his report of 49 cases. He attributed the unusually long duration of these four cases to the existence of a benign type of the disease rather than to any effects of treatment. Fowler<sup>6</sup> states that rare instances in which

TABLE II  
Cases of Chronic Leukemia of Particularly Long Duration

Author	Type	No.	Years Duration	Duration Calculated from	Treatment
Craver <sup>4</sup>	Lymphatic	1	12 or 13	Onset of symptoms	X-ray
Forkner <sup>5</sup>	Myelogenous	1	18	Date of diagnosis	None
Hoffman and Craver <sup>11</sup>	Myelogenous	4	11, 12.5 16, 16.5	Onset of symptoms	Only during last ½ to 1½ years
Jackson <sup>14</sup>	Lymphatic	2	10, 12	Date of diagnosis	X-ray
Leavell <sup>17</sup>	Lymphatic	1	16	Date of diagnosis	
Lawrence et al. <sup>16</sup>	Myelogenous	3	9,* 10*	Onset of symptoms	P <sup>32</sup> alone or with x-ray
Lawrence et al. <sup>16a</sup>	Lymphatic	4	20,* 12,* 12,* 11	Onset of symptoms	P <sup>32</sup> alone or with x-ray
McGavran <sup>22</sup>	Lymphatic	1	25	Date of diagnosis	X-ray during last 15 yrs.
Minot and Isaacs <sup>25</sup>	Lymphatic	3	11, 15, 22	Date of diagnosis	No irradiation
Richards and Moench <sup>22</sup>	Lymphatic	1	16	Date of diagnosis	None
Rosenthal <sup>22</sup>	Myelogenous	1	16		
Widmann <sup>40</sup>	Lymphatic	2	13, 18	Date of diagnosis	X-ray
	Myelogenous	2	13, 19	Date of diagnosis	X-ray

\* Patient still living.

chronic myelogenous or lymphatic leukemia has been present for 15 to 20 years have been recorded but that this exceedingly benign form is not common. Forkner<sup>5</sup> had a patient with chronic myelogenous leukemia who showed a white blood cell count of about 30,000, with many myelocytes and myeloblasts, for 18 years without any specific treatment. Lawrence et al.<sup>16, 16a</sup> have several patients with very long duration now under observation.

### REMISSIONS

In the course of leukemia, remissions, both symptomatic and hematologic, may occur spontaneously as well as from the effects of treatment. Such spontaneous remissions may contribute to the long duration of many of the unusual cases under discussion but no cause—other than natural variation in the disease—has ever been definitely established for their occurrence. Forkner<sup>5</sup> states that patients may frequently remain in a more or less stationary phase for several years but that complete spontaneous remission has never been recorded in chronic leukemia. Minot and his associates<sup>24, 25</sup> described spontaneous remissions of moderate degree in 7.7 per cent of their series of patients with chronic myelogenous leukemia and 5 per cent of cases with the chronic lymphatic variety. None of these patients had been irradiated. Sturgis<sup>35</sup> estimates that spontaneous remissions occur in less than 10 per cent of patients with chronic myelogenous leukemia. Pierce,<sup>29</sup> Marcus,<sup>21</sup> and Whitby and Christie<sup>39</sup> have also described cases with remissions of varying duration and completeness. Jackson<sup>11, 12, 13</sup> has described two cases of temporary complete remissions, both clinical and hematological, in acute leukemia, each lasting five months. One remission followed the administration of yeast adenylic acid and the other followed the administration of pentnucleotide to a child who had developed otitis media and lip necrosis as complications of measles and acute lymphatic leukemia, but both were considered to be of spontaneous origin. Moeschlin<sup>27</sup> has been quoted by Bethell et al.<sup>3</sup> as reporting several unusual remissions in myelogenous leukemia. In one of his cases three remissions occurred in the 16 month course of one case and the marrow obtained by sternal puncture appeared normal during a remission. The remission in Rappoport and Kugel's case<sup>30</sup> of monocytic leukemia is also noteworthy because of serial marrow examinations. On first examination, the marrow suggested leukemia. During remission the marrow differed but slightly from normal and the previous provisional diagnosis of leukemia could not be substantiated. Subsequently the marrow became characteristic of monocytic leukemia and the patient died of the disease.

### EFFECTS OF INFECTION

Various types of infection have been reported as a cause of remission in leukemia. Infection might, therefore, be a factor in cases of long duration. Forkner<sup>5</sup> reviewed the pertinent literature and concluded that, although many miscellaneous infections were associated at times with evidences of

regression, in all instances in which recovery from infection occurred leukemic manifestations recurred, usually in a few weeks. Wintrobe and Hasenbush<sup>41</sup> stated that "contrary to the opinion frequently expressed, infections in the great majority of the cases did not produce a remission in the physical signs or in the blood picture." In four of their cases, infections actually caused an increase in white blood cell count. Heinle and Weir<sup>9</sup> describe the morphologic obliteration of a case of chronic myeloid leukemia by active tuberculosis and discuss the inter-relations of leukemia and tuberculosis. The relationships of these two diseases are also discussed by Ulrich and Parks.<sup>36</sup>

### EFFECTS OF TREATMENT

It is generally agreed<sup>11, 15, 16, 16a, 20, 24, 25, 28, 40</sup> that there is not yet clean cut evidence that treatment has significantly prolonged the duration of any type of chronic leukemia. However, practically all agree that radiation therapy lengthens the period of comfortable and useful life. The possibility of cure of leukemia is still undetermined. Until more is known about the etiology of leukemia, it can not be stated definitely whether recovery is possible. Certain conditions may simulate leukemia. Washburn<sup>38</sup> treated a case of chloroma with excision and radiation. The patient showed myeloblasts and myelocytes in the blood and lesions in bones other than the one removed surgically. The patient was well two and a half years after the operation. This case was reviewed in 1941 by Washburn and Christie<sup>38</sup> at the completion of 15 years of follow-up. At that time the patient was in fairly good general health, had normal bones on roentgen-ray examination, and exhibited no blood abnormalities. The authors concluded that it was impossible to say whether the patient had either xanthoma or chloroma. One can therefore not accept this case as a cure of leukemia. Lecène<sup>19</sup> is quoted by Forkner<sup>5</sup> as reporting a possible two year cure of a case of localized chloroma. Lebon<sup>18</sup> and Schiassi<sup>34</sup> each reported cases cured or long-arrested by roentgen radiation according to Forkner.<sup>5</sup> Herz<sup>10</sup> recorded the case of a physician of 27 who apparently recovered from acute leukemia. The patient exhibited malaise, fever, ecchymoses, necrotic tonsils, cervical and axillary adenopathy, and splenomegaly. Hemoglobin was reported 85 per cent, red cell count 4.5 million, platelets reduced, and white cell count 18,000, with 50 per cent myeloblasts. The author evidently believed mononucleosis was ruled out by differential staining reactions but unfortunately the case preceded the development of the Paul-Bunnell test. The sternal marrow was evidently not examined. Herz concluded that acute leukemia was not necessarily fatal and that the diagnosis need not be discarded if the patient recovered. Gloor<sup>7</sup> has reported the case of a 49 year old businessman who had fever, swollen, ulcerated, bleeding gums, enlarged tonsils and cervical nodes, hepatomegaly and splenomegaly, anemia (hemoglobin 51 per cent, red blood cells 2.76 million), and a white blood cell picture of acute

leukemia (white blood cells 15,800 with 91 per cent myeloblasts) when first seen. After therapy with roentgen-ray, arsenic, intravenous mesothorium, transfusions, and iron, a marked leukopenia (white blood cells 955) developed and myeloblasts disappeared from the peripheral blood. Two months later the blood picture was normal and it remained so two years later although slight splenomegaly persisted. Platelet counts were not discussed and the sternal marrow was apparently not examined.

Minot's patient<sup>26</sup> exhibited anemia, thrombopenia, and a leukocyte pattern indistinguishable from acute leukemia but recovered without special treatment. The case is recorded in detail and should be acceptable as a cure if any case of leukemia is to be recognized as cured, but Minot describes it as a case "simulating" leukemia with recovery.

These and other reports of alleged cures of leukemia were reviewed by Forkner.<sup>5</sup> He believed that only a few of the reported cases had been studied adequately for evaluation but that a few patients who presented a picture identical with that of leukemia had recovered. Moeschlin,<sup>27</sup> quoted by Bethell et al.,<sup>3</sup> however, concluded that "a critical review of the literature fails to disclose a single well-authenticated case in which leukemia was actually cured."

### PROGNOSIS

Pascucci<sup>28</sup> summarized the factors which were associated with short duration of the disease in his series of 128 patients from the Presbyterian Hospital in New York. He listed the following findings as indicating a poor prognosis, but stated there were few substantiating statistics: very high or very low white blood cell count, serious anemia, high number of blast cells, excessively high or excessively low platelet count, marked splenomegaly, diffuse lymph node involvement, presence of complications (hydrothorax, pneumonia, tuberculosis, osteomyelitis, cardiovascular disease, etc.) and short duration of symptoms prior to diagnosis. It was suggested that the patients with a short duration of symptoms prior to diagnosis had a less chronic form of the disease.

Leavell<sup>17</sup> discussed several factors affecting the prognosis at the original examination. The prognosis was better in chronic lymphatic leukemia with onset between the ages of 40 to 60 years but seemed unaffected by age of onset in chronic myelogenous leukemia. The presence of anemia led generally to a poor prognosis, particularly in lymphatic leukemia, but one patient was mentioned who lived 16 years after being seen with a hemoglobin of 45 per cent. The height of the leukocyte count was of some prognostic significance in that patients with myelogenous leukemia tended to do poorly if they originally showed a relatively low white cell count whereas those who had lymphatic leukemia lived somewhat longer if the original leukocyte level was relatively low. Bleeding manifestations at the original examination were usually associated with short duration of the disease.

Lawrence and his co-workers<sup>10, 16a</sup> observed that it was not possible to predict which patients would have a long duration of their disease but that since with present methods of treatment over one third of these patients survive five years or longer, it must be assumed by the physician that any individual patient under treatment will fall into this group. Actually the five year survival figures are good when compared to those of cancer of the esophagus, stomach and lung, and many other neoplasms in the more advanced stages.

### PARTICULARLY CHRONIC FORM

Many authorities have "explained" the long duration of certain cases of chronic leukemia by assuming that there exists a particularly chronic form of the disease. To state that cases of long duration have a long duration gives no real explanation for the phenomenon, nor does it help us to select in advance those cases which will eventually turn out to belong to the particularly chronic variety. Haden<sup>8</sup> has noted that chronic lymphoid leukemia is often very mild and runs a benign course. Minot and his co-workers stated<sup>24</sup> that "many . . . patients had symptoms for a long time prior to therapy and were recognized as having the type of case that progressed sluggishly." Pascucci<sup>28</sup> wrote: "Chronicity, measured by the duration of symptoms before the patient seeks medical aid, has a definite bearing on survival: the more chronic the disease, the longer is the life expectancy." He showed the following survival periods in relation to duration of symptoms before treatment.

Duration Symptoms Before Treatment	Myeloid		Lymphatic	
	Years	Patients	Years	Patients
6 months	2.2	31	1.8	18
6 months to 1 year	2.3	11	2.3	18
1 to 2 years	3.1	5	2.7	11
2 years or over	3.9	5	5.0	12

Widmann<sup>40</sup> stated: "The four instances in this series (vide supra) of an unusually long life may be the effect of a very benign character of the disease and not attributable directly to irradiation."

### CASE REPORTS

From a total of approximately 190 cases of chronic myelogenous and chronic lymphatic leukemia seen and treated at the Crocker Laboratory since 1937, we have selected 31 cases of particularly long duration for presentation. With the passage of time the number in this group will become larger since many of these patients have been first seen during the past few years. The patients selected were those who had lived five years or more after the diagnosis had been established by blood counts.

The much larger group of patients living five years after onset of symptoms was not included. These cases are summarized in tables 3 (Chronic Lymphatic) and 4 (Chronic Myelogenous Leukemia). It is of interest that two-thirds of our patients with myelogenous leukemia who lived over five years from the date of diagnosis were women whereas there was only one woman in our series of long-lived patients with lymphatic leukemia. These findings suggest that a hormonal factor may be operative in some patients with long duration. In our experience approximately 70 per cent of patients with lymphatic leukemia are males and 60 per cent of those with myelogenous are males. With the passage of time the number of patients in this series will increase.

The age of onset is tabulated in the third column of tables 3 and 4. The average values correspond with Minot's findings<sup>24, 25</sup> and that of our complete series<sup>16, 16a</sup> for the age incidence of leukemia but there is considerable individual variation. As stated above, in our patients with lymphatic leukemia those with onset between the ages of 30 to 40 have the longest duration.

The seven patients in table 3 and three patients in table 4 whose age at death is not recorded in column four were alive at the time of writing this report (May, 1948). All 10 were doing very well at the last examination. Six in the lymphatic group and two in the myelogenous group have had no treatment for two or more years.

Duration of the disease is listed in the next three columns of both tables. The date used for onset of symptoms was that from which symptoms could be definitely attributed to leukemia. Some patients gave histories of vague or general symptoms preceding the actual date used but these were disregarded in the interests of accuracy. The next eight columns tabulate the earliest findings now available to us. As noted in the first column of this section, the original blood counts on which the diagnosis was based are not available to us in every case but where they are not, the time interval which elapsed between diagnosis and the first count recorded in our records is noted. In accord with Pascucci's<sup>28</sup> and Leavell's<sup>27</sup> lists of factors affecting prognosis which have been referred to above, it will be noted that few of the patients who lived long with lymphatic leukemia had significant anemia at the onset but case JFP, who is now alive with normal total blood cell counts, had a significant degree of anemia 11.6 years ago. More marked anemia was a common early finding in the group of the myelogenous type.

Original white blood counts varied widely but there were none with leukopenia and none higher than 300,000 in the lymphatic or 500,000 in the myelogenous groups.

Abnormal differentials were of course present at the original examination which established the diagnosis but the per cent of immature cells in the myelogenous series was low and few of these abnormal cells were blasts. This was another factor of prognostic significance which Pascucci listed.<sup>28</sup>

Splenomegaly was marked at the onset of three of the myelogenous cases and lymphadenopathy marked from the beginning in four of the lymphatic cases. These findings are ordinarily thought to connote a poor prognosis. In several cases the early physical findings were not reported to us.

Three columns in each table list the treatment given to these patients throughout the course of their illness. The treatment in most of these cases has been so varied that an analysis of its effect on duration would not be of value. Although our treatment has been chiefly with radioactive phosphorus (P-32) occasionally supplemented with roentgen-ray, a few of these patients had been treated previously with roentgen-ray or Fowler's solution while not under our supervision. The total dose of P-32 given (column 16) accordingly depends more on how long the patient was under our immediate supervision than it does on the severity of his leukemia. It is of interest, however, that eight patients (four with lymphatic and four with myelogenous) who lived five years or more after the diagnosis of leukemia were treated with radioactive phosphorus only.

TABLE III  
Chronic Lymphatic Leukemia

Case	Sex	Age		Duration in Years from			Early Findings								Treatment			Late Findings							
		Onset Symp.	Death	1st Symp.	Diag.	1st Rx	Years after Diag.	Hg %	RBC $\times 10^6$	WBC $\times 10^3$	% Abn. (% Lymph.)	Spleen	Liver	Nodes	Pa. mc.	X-ray Courses	Other	Years after Diag.	Hg %	RBC $\times 10^6$	WBC $\times 10^3$	% Abn. (% Lymph.)	Spleen	Liver	Nodes
FAB	M	39	—	7.6	7.6	7.5	0.0	82	4.50	148	96	0	0	Slt.	30	2	0	7.6	90	4.34	17	90	0	0	Slight
FMB	M	56	67	11.2	10.5	10.4	0.0	80	5.01	39	94	Mod.	0	Mod.	27.3	2	0	8.7	72	3.74	18	89	0	Mod.	
AB	M	49	57	7.8	5.8	5.8	0.0	80	4.55	53	95	*	*	Mkd.	11.9	2	Fowler's	5.0	84	3.74	18	75	0	Mkd.	
BC	M	34	40	6.6	6.3	3.7	0.0	97	4.94	34	64	Mod.	*	Mkd.	30.9	0	0	6.6	25	1.15	71	99	#	#	
LPD	M	50.3	—	19.7	19.0	19.0	4.0	100	5.00	70	98	Slt.	0	0	18.5	Many	0	19.0	92	5.42	19	85	0	0	
FE	M	40	—	5.3	5.3	5.3	0.4	87	4.48	21	81	0	0	Mod.	8.8	1	Fowler's	5.3	110	5.10	14	69	#	#	
KCG	M	36	42	5.4	5.4	1.5	0.0	*	*	46	*	*	*	Mkd.	7.4	2	0	5.4	69	3.89	22	90	#	Mkd.	
GEH	M	66	73	7.9	7.9	7.9	0.0	81	4.28	170	95	Slt.	*	Slt.	52.8	Many	Benzine	7.8	47	2.30	73	94	#	Mkd.	
FHL	M	65	74	9.0	9.0	7.0	0.0	*	*	20	60	*	*	0	28.4	2	Fowler's	9.0	60	2.75	14	76	#	#	
FWL	M	55	62	7.3	6.8	6.8	0.5	107	5.62	43	77	0	0	Mod.	48.1	1	Fowler's	6.8	#	2.00	246	97	Slight	Slight	
JFP	M	35	—	11.6	11.6	11.5	0.0	70	3.17	21	90	0	0	0	10.0	0	Fowler's	11.6	104	4.86	9	68	0	0	
MP	F	59	—	7.2	7.2	7.0	0.2	90	5.56	92	81	Slt.	0	Slt.	22.7	0	0	7.2	98	5.09	30	81	0	Slight	
BJP	M	54	—	6.0	6.0	6.0	1.5	90	4.68	294	96	Slt.	0	Mod.	42.8	0	0	6.0	85	4.70	26	57	0	Slight	
CWR	M	50	55	5.4	5.4	5.4	0.0	*	*	25	*	*	*	*	19.2	Many	*	5.2	30	1.65	331	#	#	#	
CRR	M	43	49	6.3	6.3	6.3	0.0	70	3.65	115	94	Mkd.	1	Mkd.	17.4	Many	Fowler's	6.3	#	#	21	#	#	#	
GLS	M	37	—	11.6	10.6	7.8	0.0	110	5.27	18	70	Slt.	Slt.	Mod.	23.0	0	0	8.3	104	5.16	23	78	Slight	0	
Av. 1 F 15 M		48	57.7	8.44	8.16	7.4		88	4.67	93	85							7.86	76.4	3.73	64.8	82			

\* Seen elsewhere—Data not available.

# Followed by other M.D. or clinic—Data not available.



TABLE IV  
Chronic Myelogenous Leukemia

Case	Sex	Age		Duration in Years from			Early Findings							Treatment			Late Findings								
		Onset Sympts.	Death	1st Symp.	1st Diag.	1st Rx	Years after Diag.	Hg %	RBC $\times 10^6$	WBC $\times 10^3$	% Abn.	Spleen	Liver	Nodes	Pz mc.	X-ray Courses	Other	Years after Diag.	Hg %	RBC $\times 10^6$	WBC $\times 10^3$	% Abn.	Spleen	Liver	Nodes
IA	F	49	54	5.5	5.1	5.0	0.1	48	2.96	455	31	Mod.	*	*	26.0	Many	0	5.0	66	3.20	86	22	Mod.	Mod.	0
DEF	F	35	40	5.3	5.3	4.4	0.0	54	3.10	305	15	Mkd.	0	0	14.3	Many	0	5.3	47	2.46	136	53	V. Mkd.	Mod.	0
MG	M	39	45	5.9	5.9	5.3	0.0	70	3.80	35	8	0	Slight	0	50.0	Many	Fowler's	5.9	70	3.09	82	47 (blasts)	V. Mkd.	Mkd.	0
FG	F	20	26	6.0	6.0	6.0	3.5	76	4.39	94	*	Mkd.	*	*	7.0	Many	Fowler's	6.0	73	3.67	9	30	#	#	#
EH	M	32	36	6.0	6.0	6.0	3.0	57	3.43	249	45	Mkd.	*	*	13.0	Many	0	6.0	75	3.60	46	28	Mkd.	#	#
MLI	M	43	—	5.6	5.6	3.8	0.0	90	4.60	228	30	Mkd.	Slight	0	23.7	0	0	5.6	80	4.35	17	12	Slight	0	0
IJ	F	44	—	6.8	6.6	6.6	0.0	68	3.40	110	17	Mod.	Slight	0	58.6	0	0	6.6	86	3.68	68	11	Mod.	Slight	0
WOJ	F	29	35	5.2	5.0	4.9	0.0	70	3.72	127	24	0	0	0	43.6	0	0	5.0	30	1.0	100	#	#	#	#
CK	M	27	36	9.0	9.0	8.8	0.2	86	3.42	200	20	Mod.	Slight	0	49.1	Two	0	8.8	60	3.65	13	69	Mkd.	#	#
ALV	F	52	60	8.8	7.6	7.2	0.4	75	3.13	208	33	Slt.	Slight	0	42.9	Many	0	7.6	56	3.13	11	50 (blasts)	Mkd.	Slight	0
PM	F	11	—	8.3	8.3	8.1	0.0	87	4.75	65	39	Mod.	0	0	22.9	0	0	8.3	97	4.84	11	1	0	0	0
JM	F	53	59	6.3	6.3	6.3	0.0	*	*	268	15	0	0	0	77.4	Many	0	6.3	59	3.25	145	33	Mod.	Mod.	#
MGM	M	26	32	5.5	5.5	5.5	3.0	80	4.00	310	*	Mod.	0	0	19.5	Many	0	5.5	85	4.47	26	16	Mod.	0	0
THM	F	53	59	6.8	6.8	6.6	3.4	*	*	30	10	Slt.	*	*	1.1	Many	0	6.8	39	2.04	17	50 (blasts)	Mod.	Slight	0
EP	F	32	38	6.0	6.0	6.0	4.5	90	4.55	20	13	*	*	*	10.5	Many	0	6.0	34	1.97	0.8	#	#	#	0
Av. 10F = 67% 5M = 33%		36.3	43.3	6.47	6.33	6.03	—	73	3.79	180.8	23							6.3	63.8	3.23	51.2	34			

\* Diagnosed elsewhere—Data not available.  
# Followed elsewhere—Data not available.

The last eight columns in each table list the latest findings available in each case. It will be noted that many patients developed anemia terminally, as one would expect, but that a number were alive with very satisfactory blood counts many years after their diagnosis was first made. Seven of the myelogenous group developed terminally an acute phase with fever, gastrointestinal disturbances, and many myeloblasts in the peripheral blood. This is a common terminal picture in chronic myelogenous leukemia.

Four patients have exhibited prolonged remissions following treatment. In two patients (MLI and PM, table 4) with myelogenous leukemia these remissions were characterized by the complete absence of abnormalities on physical examination and by normal total blood counts, although an occasional myelocyte could be found in blood smears, for three years.

Infection has apparently played no part in the long duration of these cases. Repeated blood examinations have shown no constant changes of significance during the course of intercurrent infections. Two patients with the lymphatic type (FAB and BC, table 3) have each had pneumonia on two occasions without any definite change in the leukemic process. One patient (FWL, table 3) made a satisfactory recovery following appendectomy for acute appendicitis and another (JM, table 4) recovered from cholecystitis and cholelithiasis after cholecystectomy with no apparent alteration in their leukemia. In passing, it is of interest to note that recently we have had develop a complicating carcinoma of the uterus in a 60 year old woman with chronic myelogenous leukemia, under treatment for over five years. Now three months after hysterectomy, this patient is normal physically and hematologically and only after careful search can a rare myelocyte be found in the blood smears.

### SUMMARY

The literature of chronic leukemia of long duration is reviewed and 31 such cases treated and observed by us are reported and analyzed. It is concluded that many patients with this disease respond well to treatment and have relatively long comfortable lives.

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# PRIMARY CARCINOMA OF THE LIVER— 25 YEAR STUDY \*

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IN 1932 Drs. Strong and Pitts<sup>1</sup> presented in detail 12 proved cases of primary carcinoma of the liver. Only those cases confirmed by necropsy and by microscopic examination of sections of the liver were included. These cases consisted of 10 Chinese and two whites, all of whom were males, seen on the wards and examined post mortem at the Vancouver General Hospital during the years 1920 to 1931 inclusive. The present report contains the findings of 43 additional cases seen in the same hospital from 1932 to 1944 inclusive. Thus, altogether this is an analysis of 55 proved examples of primary hepatic malignant disease seen during a 25 year period.

TABLE I  
Analysis of 55 Cases of Primary Carcinoma of Liver

	White		Chinese		Japanese		Total
	M	F	M	F	M	F	
Previous report 1920-1931	2		10				12
Present report 1932-1944	15	1	25		2		43
Total, 1920-1944 inc.	17	1	35		2		55
		Hepatoma		41			
		Cholangioma		14			

Of the 43 new cases being discussed (table 1), 25 are Chinese males, two are Japanese males, 15 are white males and one is a white female. When these are added to those previously reported, the final totals are 35 Chinese males, two Japanese males, 17 white males and one white female. There would appear to be an increasing incidence among whites, for in the first report whites comprised only 16.6 per cent of the cases, and in the total series the percentage of whites had risen to 37.2 per cent of all cases. It is to be noted that as in other series the finding of primary carcinoma of the liver in white women is very rare. The occurrence of a large number of cases of primary carcinoma of the liver in Chinese men without any in Chinese women is probably not significant since we see very few Chinese women in the Vancouver General Hospital.

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The present series of 43 cases consisted of 33 hepatomas and 10 cholangiomas, and when these are added to those previously reported, the total figures show 41 primary carcinomas of the hepatoma type and 14 of the cholangioma type. Mention has been made before of the frequent association of hepatic cirrhosis and primary hepatic carcinoma, and our findings confirm the fact that these two conditions occur together in almost every case.

As indicated in our previous report,<sup>1</sup> the Chinese whom we see have or have had a high incidence of infestation with intestinal parasites. The presence of these parasites may antedate by many years the development of liver disease. In our first series in none of the Chinese was the liver fluke, *Clonorchis sinensis*, demonstrated at the time of necropsy, but we presumed that such infestation might have led to a hepatitis, then a cirrhosis, and finally a primary carcinoma. In the present series the parasite was found in four Chinese at autopsy. The relation of the liver fluke to chronic liver disease including primary cancer would seem to merit consideration, though there is no evidence that among the whites intestinal parasites of any sort played any part in the etiology.

TABLE II  
Incidence of Primary Carcinoma of the Liver  
(Necropsy)

	No. of Cases	No. of Necropsy	Percentage Incidence
1920-1931			
White	2	1828	0.109%
Chinese	10	139	7.18%
Japanese	—	—	—
Total	12	1967	0.61%
1932-1944			
White	16	7340	0.26%
Chinese	25	446	5.44%
Japanese	2	—	—
Total	43	7786	1.81%
Grand total	55	9753	0.56%

The figures for incidence at necropsy of this form of malignant disease are shown in table 2. In our first report the incidence among whites was 0.1 per cent, which is about that usually reported. Among Chinese, however, the incidence was 7.1 per cent, which brought our total incidence to 0.6 per cent. In the present series of 43 cases the incidence at necropsy among whites has more than doubled to 0.26 per cent; the Chinese are not quite so high at 5.4 per cent, but the total incidence of 1.8 per cent is three times that in the earlier series. The incidence of primary carcinoma of the liver in all cases over the whole 25 year period is 0.56 per cent.

The average duration of the disease, as judged by the interval between the onset of symptoms and death, was comparatively brief; in fact, primary carcinoma of the liver is one of the most rapidly fatal of all malignant neoplasms. It matters little whether the tumor is a hepatoma or a cholangioma as far as prognosis is concerned, nor is the duration of the disease much different in the whites or Chinese. Because of the well-recognized stoicism of the Oriental there were not a few instances in which patients of this race walked into Hospital a few days before death from primary cancer of the liver. Although the duration of symptoms and signs was about the same in both races, the whites were usually bed patients for a longer period than the Chinese. The average age at death from hepatoma is 49.5 years for Orientals and 66.07 years for whites, whereas for cholangiomas it is 51.4 for the former, and 59.7 for the latter. The onset of hepatic malignant disease of both types occurs earlier in Chinese than in whites.

The symptoms of primary carcinoma of the liver are those of a rapidly progressive cirrhosis of the liver, coupled with the symptoms of malignancy, cachexia, weakness and weight loss. The whole picture of cirrhosis is foreshortened, and the portal obstruction leads to early ascites with resulting abdominal distention magnified by the associated and rapid weight loss. There were certain symptoms which distinguished this condition from cirrhosis; pain, for example, was a presenting complaint, being abdominal in 19 cases and thoracic in 11. Other common symptoms were anorexia in 15, weakness in 11, and dyspnea in eight cases. Less frequently noted were drowsiness, numbness of the feet, indigestion, constipation, nocturia and urinary retention, diarrhea and nausea.

The physical signs were of greater importance in diagnosis. The commonest sign was ascites, present in 31 cases, although some fluid in the abdomen was always found at necropsy. Hepatomegaly, which was noted in 22 cases, was the next most common physical sign. The liver is enlarged and fixed early in the disease, with the result that the right diaphragm is elevated and shows diminished respiratory movement. This diagnostic feature as determined by roentgen-ray has been of some value. Ankle edema occurred in 22, weight loss in 17, and jaundice in 10 cases. Other signs which were less frequently noted were splenomegaly, abdominal tenderness, emesis, fever, hemoptysis, hematemesis, melena, hematuria, clay-colored stools, and carcinoma cells in the ascitic fluid. In the diagnosis of primary carcinoma of the liver, a negative finding by roentgen-ray in a gastrointestinal series is of some value.

The average duration of illness has been mentioned previously. The manner in which the illness terminated is of interest. Twenty-five of the cases died a cachectic death outwardly similar to that of death due to extensive carcinomas of other systems. Very occasionally this was associated with some degree of myocardial failure, chronic nephritis, or early evidence of infection, i.e., pleural empyema or bronchopneumonia. Massive hemorrhage from a ruptured esophageal varix or an intraperitoneal hemorrhage

from an eroded vessel in the hepatic tumor nodules accounted for death in 14 instances, and an additional death was due to abdominal hemorrhage, following perforation of an omental artery by the trocar on attempting a paracentesis. One death was due to an overwhelming infection of the liver with formation of an hepatic abscess and a right-sided pleural empyema. Another death was the result of cerebral infarction subsequent to thrombosis of a cerebral artery. However, in both of these there was extensive malignant change in the liver, justifying their inclusion in this paper.

Although laboratory investigation has not been extensive, certain procedures were more or less routinely performed. The hemoglobin was invariably slightly lower in the Oriental than in the white man, but both exhibited a hypochromic normocytic anemia, and in those instances of massive hemorrhage a lower hemoglobin concentration was recorded, as would be expected. The white cell count was usually within normal limits; in those cases with a leukocytosis there was no change in the differential count. The sedimentation rate (modified Westergren) was elevated in every case in the manner which indicates existence of an active chronic disease. Examples of elevated non-protein nitrogen were quite rare. The Kahn reaction was negative.

On many occasions during the past there have been patients admitted to the Vancouver General Hospital for whom we have considered the possibility of a primary type of carcinoma of the liver in the preliminary differential diagnosis. In the light of further clinical and laboratory investigations, we have made this the final diagnosis with confidence in some of the cases here reported and had it confirmed at autopsy. There follows a presentation of two such cases, the first a male Oriental and the second a female Occidental.

#### CASE REPORTS

*Case 1.* E. F., male, aged 59, was admitted November 20, 1943 and died January 16, 1944. The *admission complaint* was moderately severe abdominal pain of three days' duration. This patient was not articulate. Through his friends, a history was obtained of intermittent attacks of epigastric and right upper quadrant pain which were of varying duration, over a period of nine months. These were not influenced by food. The attack which had precipitated this admission had begun with unusual suddenness and had rapidly reached a degree of severity which was difficult to bear. The pain was constant and was not confined to any particular quadrant. There was no associated nausea, emesis, diarrhea, or abdominal cramp. The signs and symptoms of shock were not present.

The history indicated that he had been seriously ill when a child in China, but since coming to Canada in 1912 had experienced no incapacitating illness.

Functionally, the man had no complaints referable to any of his systems, with the exception of a slight degree of dyspnea on exertion.

Physical investigation was negative until the abdomen was examined. This was protuberant and showed slight edema of the abdominal wall. This superficial edema involved the entire trunk, genitals and both inferior extremities. Palpation over the entire abdomen revealed no areas of tenderness, and there was no regional muscular rigidity. The right upper quadrant and epigastrium were occupied by a smooth, firm,



non-tender mass which moved slightly in the epigastric region during deep inspiration. Upon percussion of the right thorax, there was diminished pulmonary resonance, and the area of dullness was continuous with the mass discovered in the abdomen. Conclusive evidence of free peritoneal fluid could not be obtained, and there were no further abnormalities noted in the abdomen.

Radiological and fluoroscopic procedures indicated that the right leaf of the diaphragm was abnormally high and fixed in position. It was the radiologist's opinion that the distortion was due to subdiaphragmatic rather than pulmonary causes.

Laboratory procedures showed repeated urinalyses to be consistently normal. Hemoglobin was 70 per cent. The total red blood cell count was 3,600,000. Color index was 0.91, and the red blood cell morphology was regular. Initial white blood cell count was 17,600, with 60 per cent mature polymorphonuclears, 32 per cent immature polymorphonuclears, 5 per cent lymphocytes, and 3 per cent monocytes. The sedimentation rate was 20 mm. in 15 minutes and 81 mm. in 45 minutes (modified Westergren). Subsequent white blood cell counts showed a gradual descent to a value slightly higher than normal, with a corresponding decrease in percentage of immature polymorphonuclears. The blood Kahn reaction was negative.

The temperature on admission was 99.4° F., and the pulse rate was 94. During hospitalization the temperature fluctuated from normal to a high of 102° F., and the pulse rate from normal to 104 per minute. Although it became obvious that the patient was gradually deteriorating, he only occasionally complained of high abdominal discomfort. A diagnosis of primary carcinoma of the liver was recorded.

The necropsy findings were: hepatoma type of carcinoma of the liver, hepatic cirrhosis, bilateral pulmonary congestion and edema, bronchopneumonia, myocardial degeneration, chronic passive congestion of the spleen and kidneys.

The second illustrative case is more interesting since the problem of diagnosis was complicated by the fact that primary carcinoma had never been seen previously in a woman patient. A tentative antemortem diagnosis of primary carcinoma of the liver was recorded but was never seriously considered.

*Case 2.* M. H., female, aged 51, was admitted October 23, 1944 and died December 7, 1944.

The patient was essentially well until three days prior to admission. There was at that time a rather sudden onset of moderately severe pain originating along the anterior and lateral aspects of the right rib margin. This later radiated at intervals through the chest to the back up to the region of the right shoulder. The pain was constant in character and aggravated by inspiration but not in a knife-like manner. The discomfort was not favorably influenced by light breathing or the adoption of different postures. The patient gave no sign of gastrointestinal disease of any kind prior to or during the illness. The past history was non-contributory. At the time of the first physical examination there was a questionable slight icteroid tinge to the sclerae. On auscultation of the lungs no adventitious sounds could be heard and the right base posteriorly was negative. The blood pressure was 150 mm. Hg systolic and 90 mm. diastolic. On abdominal examination only a slight degree of right upper quadrant tenderness could be found.

The temperature on admission was 102° F.; pulse rate was 80 per minute; and respirations were 20 per minute. The clinical impression was: (1) subdiaphragmatic abscess, and (2) diaphragmatic pleurisy.

Roentgenogram of the chest showed both elevation and fixation of the right diaphragm with slight signs of pleural thickening. There was no indication of active pulmonary disease. At this time the roentgen-ray diagnosis was costophrenic pleurisy, though a second radiological opinion was that the changes could be due to increased abdominal pressure.

Examinations of the blood and urine were essentially negative. The van den Bergh reaction was within normal limits.

During subsequent days the temperature showed a diurnal variation from 99° to 103° F., and diaphoresis was constantly marked. Strapping with adhesive tape, local heat, sulfathiazole, penicillin and codeine did not benefit the thoracic distress or the fever. A second roentgenogram was similar to the first, but the interpretation was that a subdiaphragmatic abscess might be present. At about this time the white blood cell count was 13,300 with 40 per cent matured polymorphonuclears, 28 per cent immature polymorphonuclears, 27 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophiles. The hemoglobin was 72 per cent, red blood cell count 3,800,000, and color index 0.94. One month following admission and following consultation with a surgeon resection of a right rib was carried out with the intention of exploring the right subdiaphragmatic space. Upon viewing the diaphragm the surgeon noted tumor nodules and the operation was terminated.

At no time during the illness did the patient feel well. Deterioration was slow but steady. Pain was constant, gradually becoming localized over the right lower chest and right upper quadrant. At the end of the second week, one of us (J. G. M.) felt a nodular, firm, slightly tender mass in the right upper quadrant and assumed it to be the liver associated with malignant involvement. The operation, of course, had produced no benefit.

At autopsy there was found primary carcinoma of the liver of the hepatoma type with extensive metastases to the periaortic lymph nodes and the nodes of the sigmoid and rectal mesentery. There was also a rather large tumor mass adjacent to the rectum. This had perforated into the rectum but had apparently produced no sign or symptom. The liver weighed 3840 grams and contained an enormous tumor growth, measuring 15 cm. in diameter in the right lobe. Numerous other nodules were scattered throughout the hepatic parenchyma. Cirrhosis was not marked.

Had these findings occurred in a man and particularly in a Chinese, the preliminary diagnosis of primary carcinoma would have been made because of the persisting right upper abdominal pain and high fixed diaphragm and diaphoresis in a patient who presented no pulmonary or pleural infection and in whom there was no intra-abdominal lesion likely to cause a subdiaphragmatic abscess.

## PATHOLOGY

Primary carcinoma of the liver presents itself in two forms: the hepatoma type, arising from liver cells; the cholangioma type, arising from bile duct epithelium. There appears to be much greater pleomorphism and polymorphism of the cells in the former type with a fair number of tumor giant cells present in many of the cases in this series.

The major distinction in the two types is the abortive attempt at bile duct formation and the relatively smaller size of the tumor cells in general in the cholangioma type. The gross tumor masses in the liver are generally bulkier in the hepatoma type.

There appears to be little question as to the relationship of cirrhosis to primary cancer of the liver, and a number of observers, chiefly Counsellor and McIndoe,<sup>2</sup> question the authenticity of a diagnosis of primary cancer of the liver in the absence of cirrhosis. It is interesting to note that in 87.2 per cent of the 55 cases here presented, cirrhosis was present. In the hepatoma type it was present in 96 per cent of the Orientals and 79 per cent of the whites, whereas in the cholangioma type it was present in 88 per cent of the Orientals and in 100 per cent of the whites.

In a previous paper<sup>1</sup> we stressed the possible association of liver fluke infestation with subsequent cirrhosis as precursors of primary cancer of the liver, as practically all of the Chinese residents in Vancouver are emigrants from the Kwantung province of China, where fluke infestation (*Clonorchis sinensis* type) is said to be practically universal, and primary cancer and cirrhosis of the liver are common. In four cases of this series the *Clonorchis sinensis* were present. These facts, we believe, are more than coincidental. However, there is still the fact that, except for one of the white patients who had lived in India for a considerable number of years, all had been lifetime residents of North America with no suspicion of any liver fluke infestation.

It was also suggested in the earlier paper<sup>1</sup> that metastases occurred almost entirely via the blood stream but, in view of the fairly frequent secondary involvement of the perigastric, preaortic, retroperitoneal, mediastinal, peribronchial and, in one instance each, the inguinal and cervical lymph nodes, this must be amended to read: "That, while metastases are chiefly hematogenous, they may also be lymphogenous in origin" (table 3).

TABLE III

No metastases	32
Lungs	16
Perigastric lymph nodes	7
Pre-aortic and retroperitoneal lymph nodes	6
Mediastinal and peribronchial lymph nodes	4
Inguinal	1
Cervical	1
Vertebrae	3
Adrenals	3
Ribs	2
Spleen	2
Brain	1
Kidney	1

Secondary deposits originating from the hepatic carcinoma were found grossly in 18 different sites. However, on the whole, liver carcinoma are quite localized, with hepatomas somewhat more than twice as invasive as cholangiomas. By far the most common sites of metastases were the perigastric lymph nodes and the lungs, and it must be pointed out that demonstrable metastases must be considered infrequent and can only rarely be used as an aid to diagnosis, i.e., by biopsy. In all of our 55 cases, a sentinel node was recorded only in one instance.

The weights of the livers in this series were much lower than those recorded in the textbooks on medicine and pathology. The average for hepatomas was 2,695 grams, with a range from 890 grams to 6,650 grams. The average weight for cholangiomas was 2,808 grams, with a range from 1,020 grams to 5,800 grams. There was little real difference between the weights of each type in males and females.

One rather interesting feature of this series is the fact that in 32 cases no metastases were found, which is most unusual in view of the marked

tendency of the tumor tissue to involve the rich vascular bed in the liver substance.

### CONCLUSIONS.

There is presented a brief analysis of 55 cases of primary carcinoma of the liver found during a 25 year period.

The clinical symptoms and signs are described and the pathologic findings noted.

Whereas it was once true that primary carcinoma of the liver could only be diagnosed at autopsy, it is now possible to make such an antemortem diagnosis with reasonable accuracy.

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# THE EFFECT ON THE PRECORDIAL ELECTRO-CARDIOGRAM OF INSULATING AREAS OF THE ANTERIOR CHEST WALL \*

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THE precordial leads have justifiably gained increasing importance in the past decade and considerable knowledge has accumulated concerning the significance of the various deflections in the standard positions. These leads are now used routinely to supplement the information given by the limb leads and, more particularly, to aid in the localization of myocardial infarcts, bundle branch block, and pathologic processes involving primarily the right or the left side of the heart. The localizing value of precordial leads results from the well known fact<sup>1</sup> that an exploring electrode on the

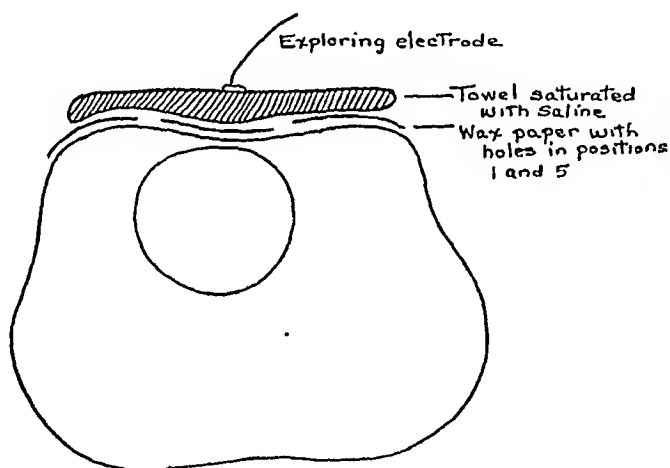


FIG. 1. Method of insulating anterior chest wall. The wet towel is in direct contact with the chest wall in the 1 and 5 positions only.

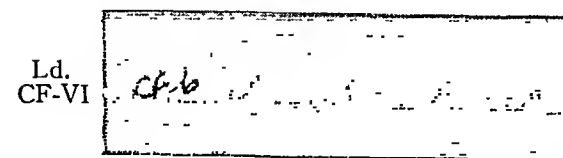
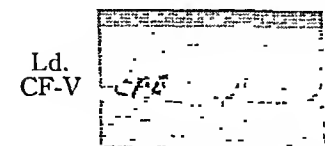
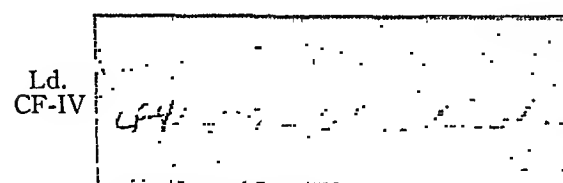
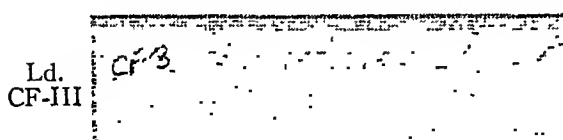
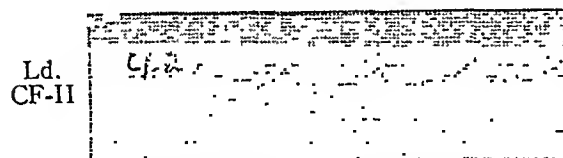
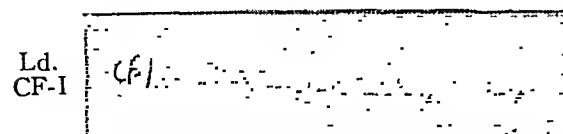
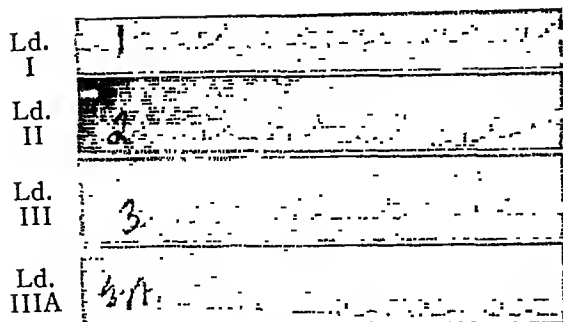
anterior chest wall produces an electrocardiogram which resembles that of the underlying epicardium and which is influenced most by the myocardium in proximity with the electrode. Thus, positions 1 and 2 on the anterior chest wall are used as indices of changes in the right side of the heart, and positions 5 and 6 are similarly used as indices of changes in the left side. The intermediate positions 3 and 4 are likely to be influenced by electrical changes from right or left and one must determine the direction of this

\* Received for publication February 19, 1948.

From the Heart Station at the U. S. Naval Hospital, St. Albans, N. Y.

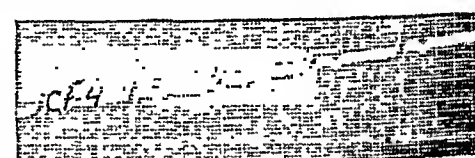
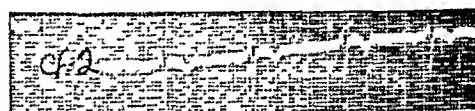
The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

## CONTROL



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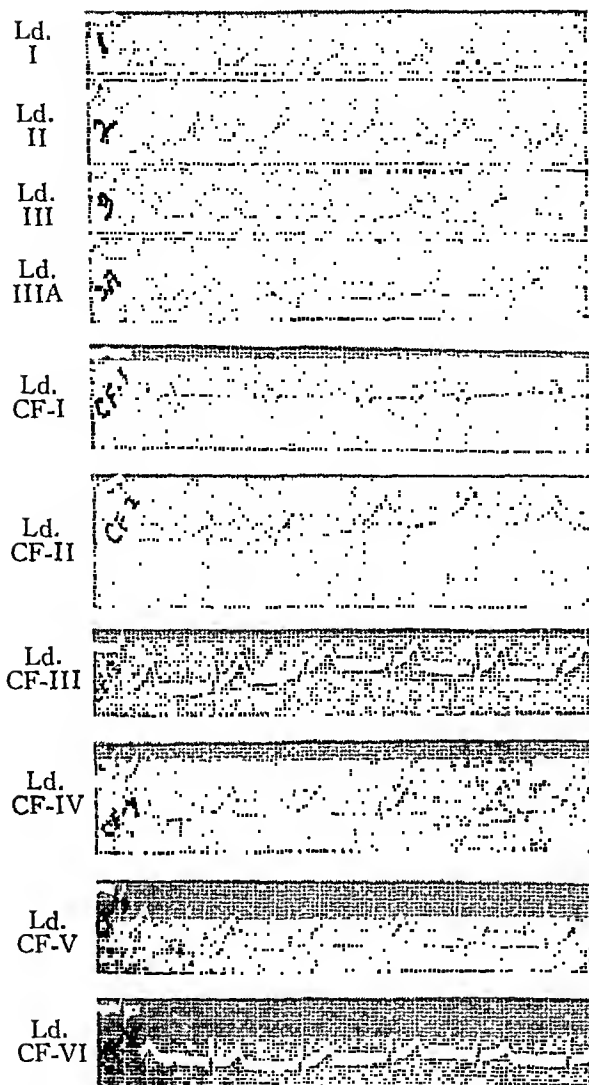
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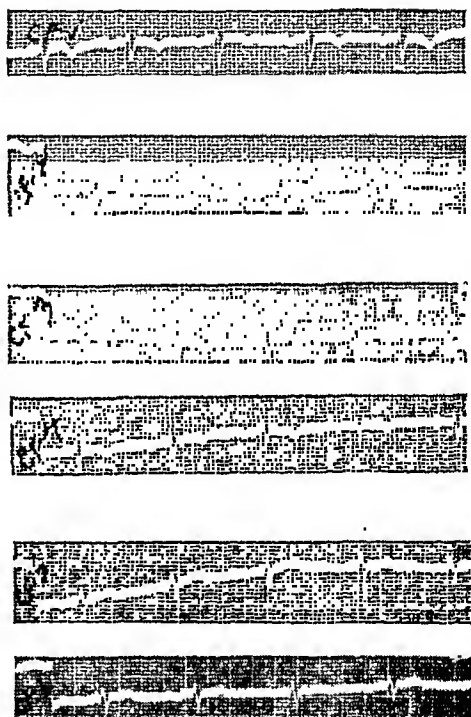
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FIG. 2. *A. Control:* A patient with no evidence of physical disease showing inverted T-wave in CF<sub>1</sub> and upright T-waves in the remainder of the precordial leads. *B. Wax paper block:* T-wave is now inverted in CF<sub>1</sub>, CF<sub>2</sub>, CF<sub>3</sub> and CF<sub>4</sub>.

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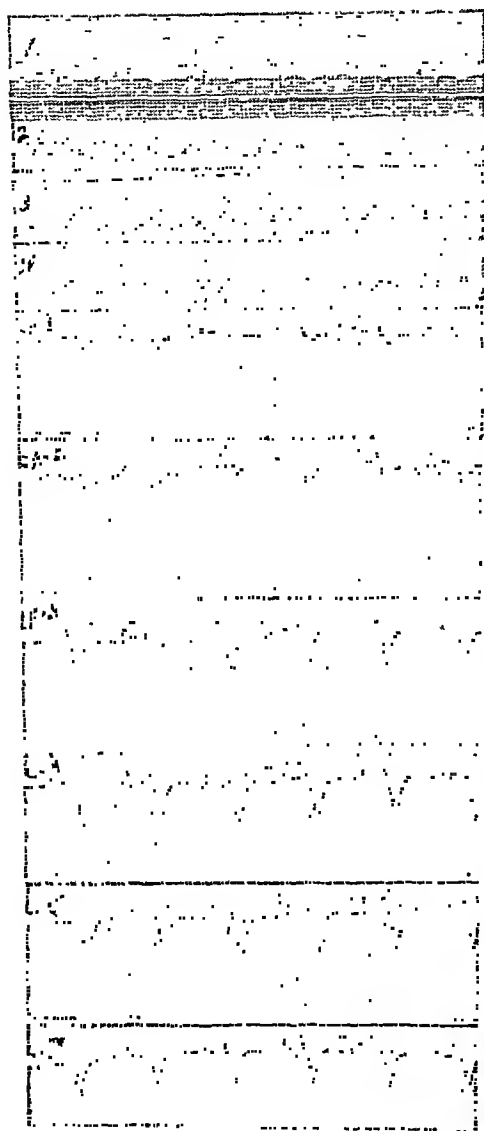
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FIG. 3. Exemplifies same changes as seen in figure 2.

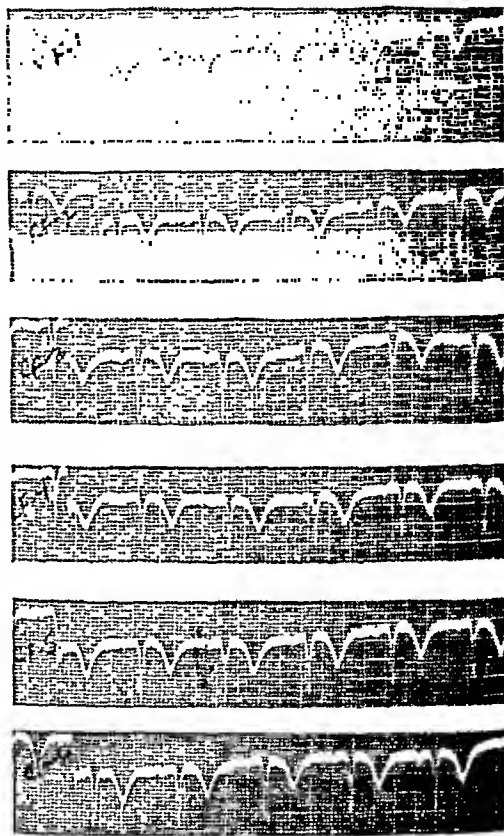
influence by comparison of these leads with the curves found in the other positions. If T-wave inversion in  $CF_4$ , for example, is associated with inversion in  $CF_5$  and  $CF_6$  while T tends to become increasingly upright in  $CF_3$ ,  $CF_2$  and  $CF_1$ , the effect is left sided. A right sided effect would, in reverse fashion, produce inversion of T in  $CF_1$ ,  $CF_2$  and possibly  $CF_3$ , with return to an upright direction in the  $CF_4$  and  $CF_5$  positions. It is evident that, if one takes just  $CF_4$ , it is impossible to decide from this precordial lead alone whether changes are the result of damage to the right or to the left. In general, when five precordial leads are taken, one can by comparison localize with accuracy. At times, however, such interpretation is rendered

## CONTROL



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FIG. 4. *A. Control:* Case of anterior myocardial infarction with inverted T-waves and an absent R deflection in  $CF_1$  through  $CF_6$ . *B. Wax paper block:* Changes similar to the control still present in the intermediate positions despite the block.

difficult or inaccurate by neutralizing effects produced on the exploring electrode in a particular position by cardiac zones that are relatively remote. In this study we have attempted to analyze such effects of remote cardiac zones in an effort to determine their relative importance and the degree to which they may distort the electrocardiographic picture contributed by the cardiac zone nearest a particular chest wall position.

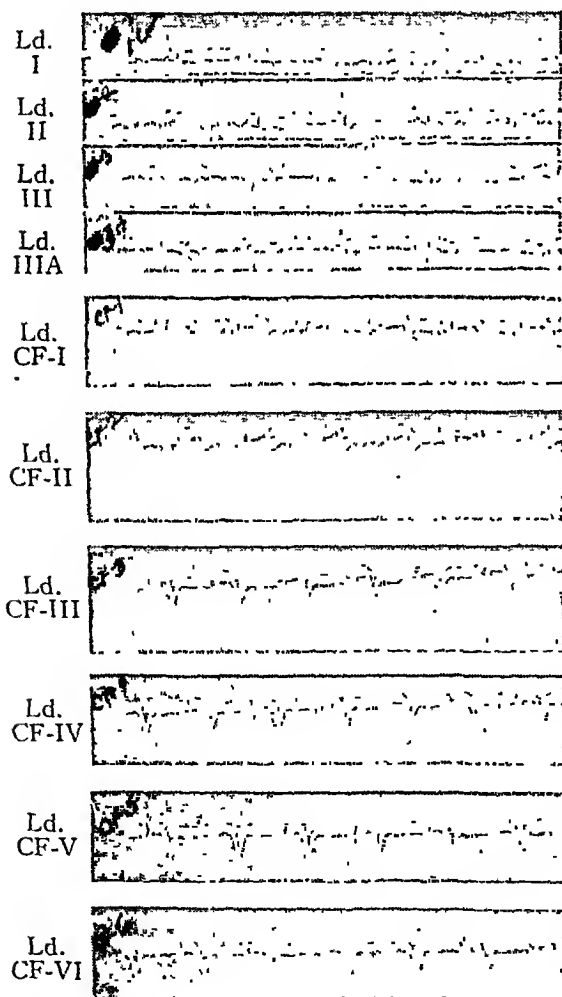
*Method:* We used wax paper on the anterior chest wall to insulate positions other than those studied. In this study we limited ourselves to in-



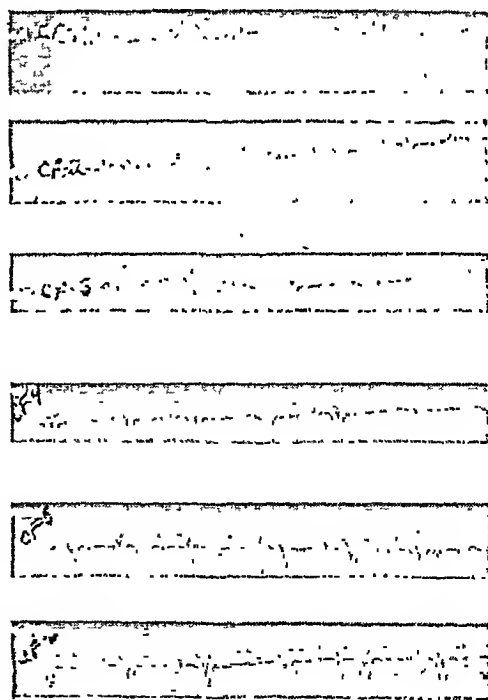
vestigation of the cardiac zones primarily responsible for the  $CF_1$  and  $CF_5$  patterns. Holes an inch in diameter, the size of the exploring electrode, were cut in the paper in the 1 and 5 positions. A towel saturated in warm saline was then placed over the wax paper and the exploring electrode was placed in succession in positions 1 to 6 on top of the wet towel. This series of electrocardiograms was compared with control tracings taken in the usual manner prior to the application of the wax paper and towelling. Figure 1 illustrates the method used. In addition to the precordial leads the three limb leads were routinely taken and also Lead III with the patient in deep inspiration, designated as 3A.

*Results:* Twenty-five subjects were studied in the manner described, including normal controls, and patients with myocardial infarction, bundle

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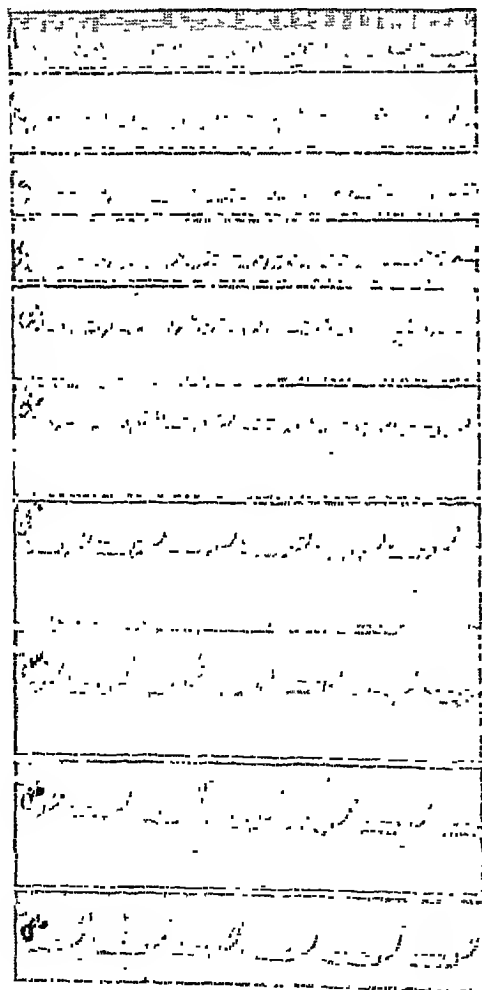
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FIG. 5. Exemplifies same changes seen in figure 4.

branch block, and patterns of left and right ventricular strain. Several typical experiments are shown in figures 2 to 9.

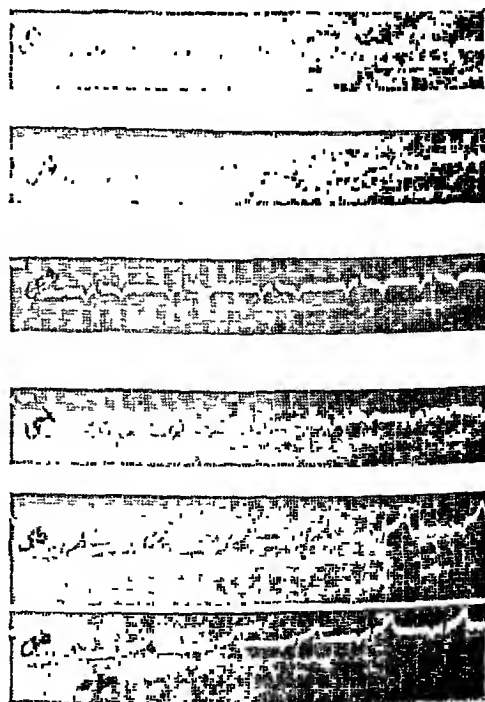
A comparison of the two sets of precordial electrocardiograms in figure 2, taken from a normal individual, shows that the insulation of the intermediate positions has caused the  $CF_1$  pattern to be carried to the left as far as  $CF_4$ . In figure 3, another normal, one finds differences in all the leads and it is of interest to observe that the QRS pattern is altered as well as that of the T-wave. Again T-wave inversion in the experimental tracings is found as far to the left as  $CF_4$ . In figure 4, taken from a patient with anterior myocardial infarction, little difference is seen in the two sets of curves except that the small R found in  $CF_6$  does not appear in the second

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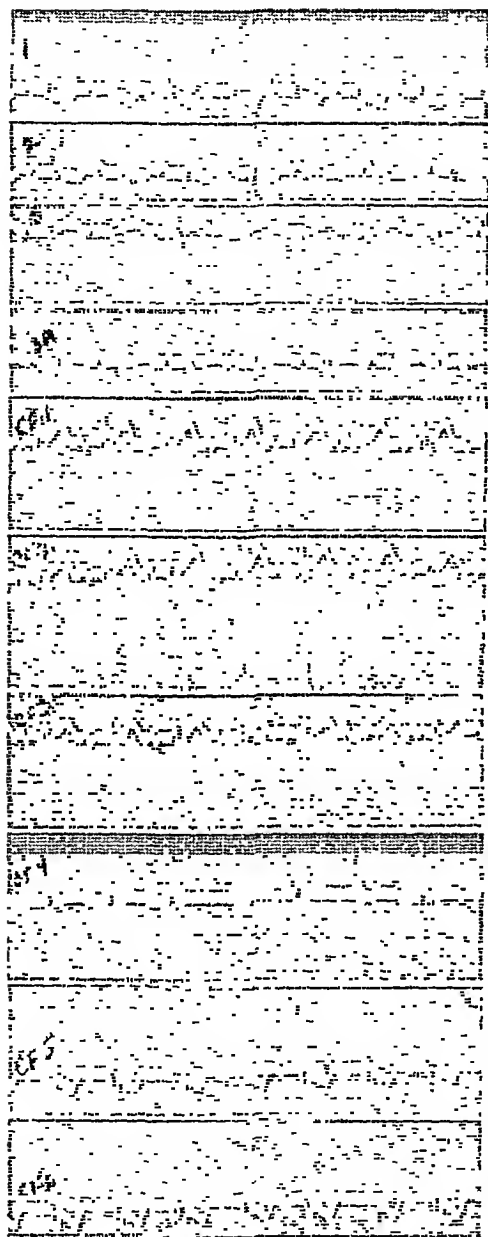


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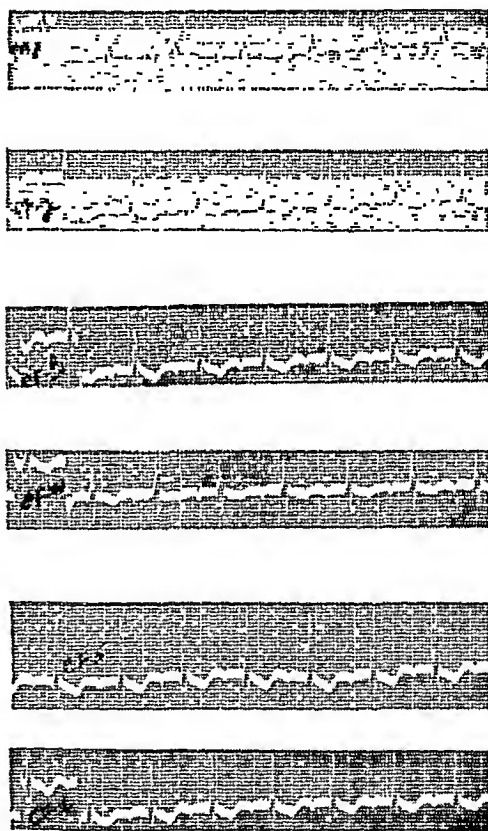
FIG. 6. *A. Control:* Case of old antero-septal myocardial infarction where the T-wave is inverted in  $CF_1$  but upright in the remainder of the precordial leads. *B. Wax paper block:* T-wave is now inverted in  $CF_1$ ,  $CF_2$ ,  $CF_3$  and  $CF_4$ .

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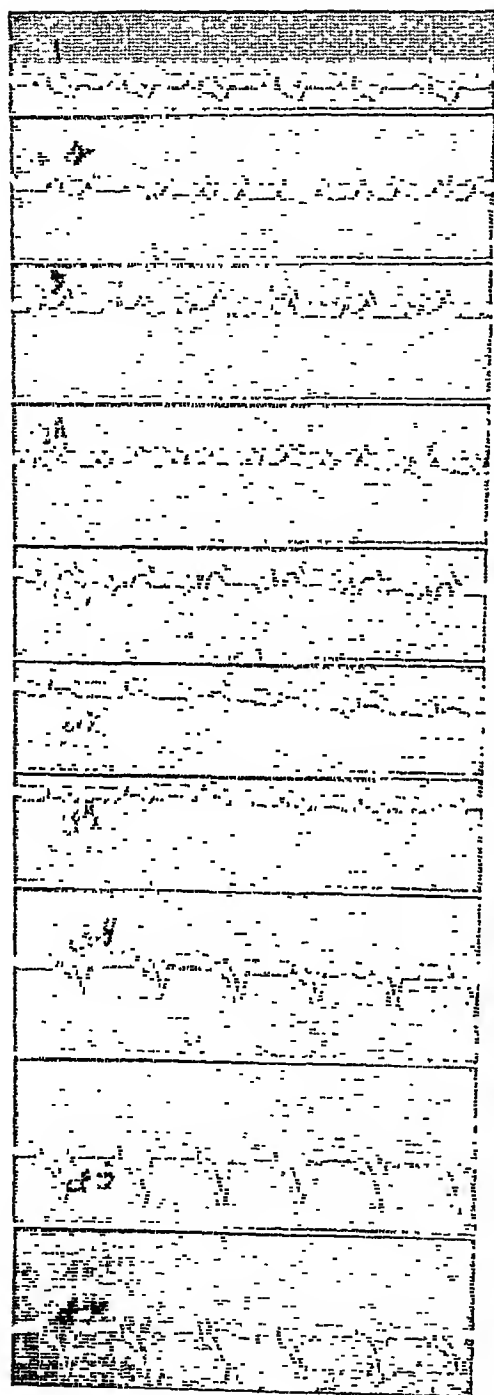


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FIG. 7. *A. Control:* Case of left heart strain with inversion of the T-wave in  $CF_5$  and  $CF_6$ .  
*B. Wax paper block:* T-wave is now inverted in  $CF_2$ ,  $CF_3$ ,  $CF_4$ ,  $CF_5$  and  $CF_6$ .

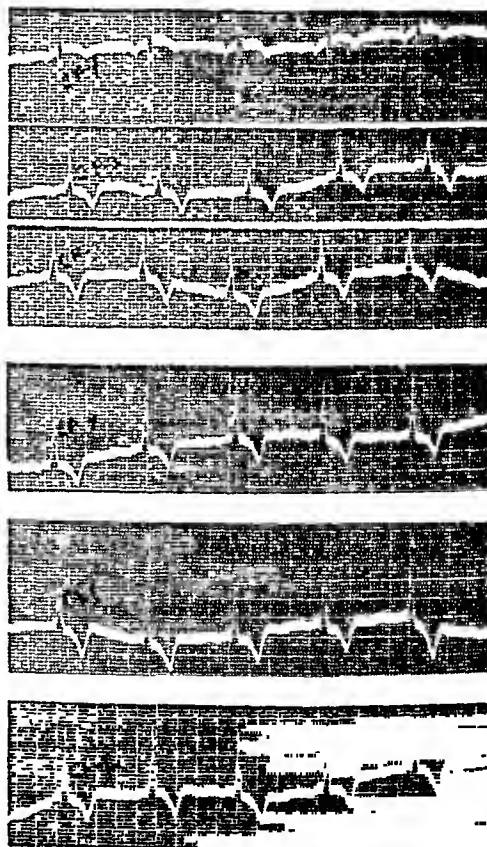
series, this position having been insulated. Figure 5 resembles the previous illustration. Here, however, the experimental curves show an R-wave in the 4 and 5 positions not found in the first series, where a notch on the descending limb of QS appears instead. This difference is probably due to the influences of cardiac zones in proximity with positions 2, 3 and 4 which

## CONTROL



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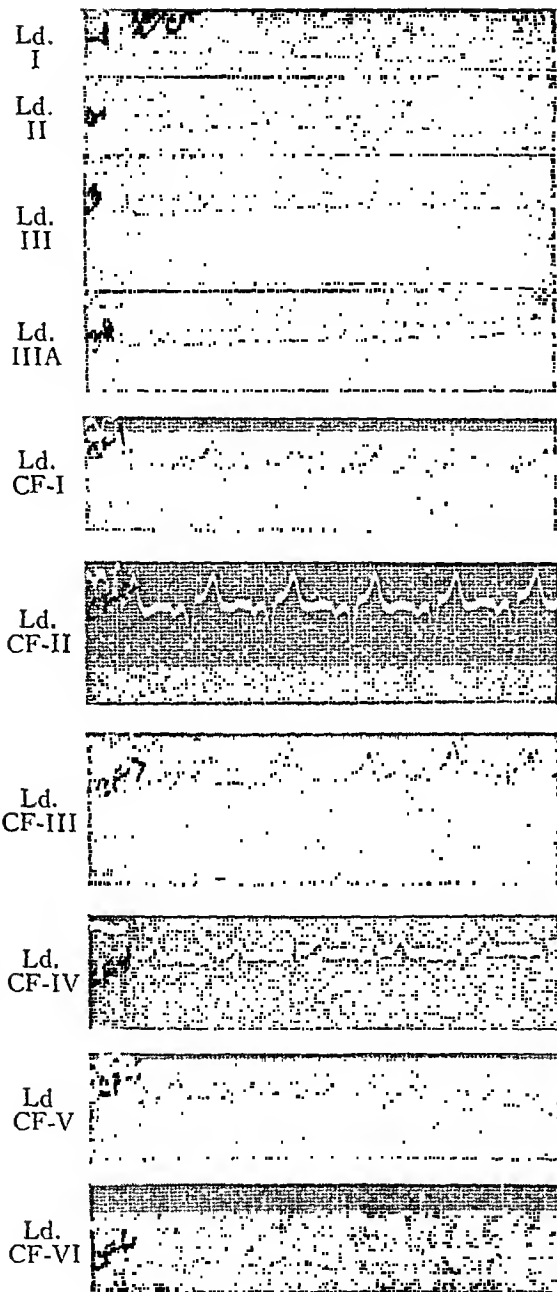
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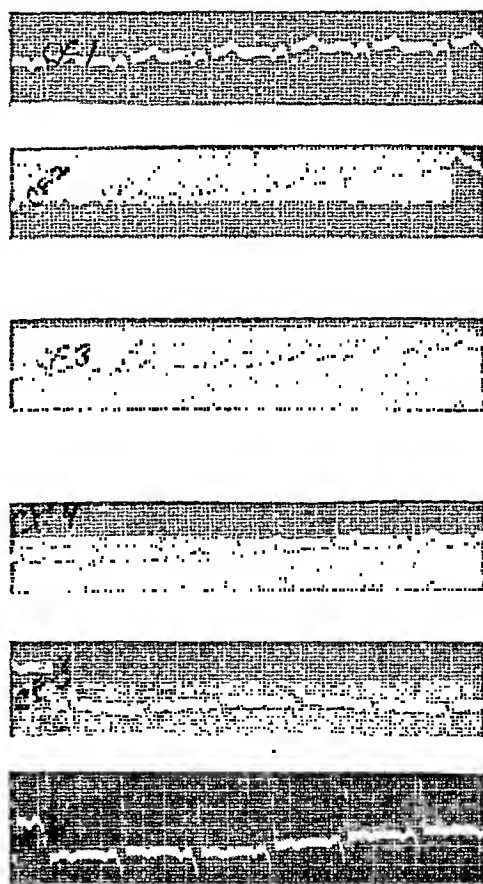
FIG. 8. *A. Control:* Case of left heart strain showing embryonic R-wave in CF<sub>1</sub>, CF<sub>2</sub>, and CF<sub>3</sub> with a prominent R-wave in CF<sub>4</sub>, CF<sub>5</sub> and CF<sub>6</sub>. *B. Wax paper block:* Prominent R-wave is now present in CF<sub>2</sub>, CF<sub>3</sub>, CF<sub>4</sub>, CF<sub>5</sub> and CF<sub>6</sub>.

## CONTROL



A

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FIG. 9. *A. Control:* Case of marked hypertension with history of a previous myocardial infarction where the T-wave was diphasic in Lead I but upright in CF<sub>2</sub> and CF<sub>6</sub>. *B. Wax paper block:* T-wave in CF<sub>2</sub> and CF<sub>6</sub> is now inverted.

have been blocked by the wax paper. Figure 6, taken from a case of old anteroseptal infarction, shows a change from an upright to an inverted T in positions 1 to 4, and, also, a reduction in the height of R in  $CF_6$ —this effect, therefore, is contributed primarily by the  $CF_6$  position which has been blocked. In figure 7, taken from a patient with left heart strain, one finds inversion of T, originally limited to  $CF_5$  and  $CF_6$ , in all positions except  $CF_1$ ; and positions  $CF_3$  and  $CF_2$  show taller R-waves—the blocked positions, therefore, have contributed deep S and positive T components. Figure 8 resembles figure 7. In this case, too, the blocked intermediate positions are shown to have contributed a negative component to the QRS and a positive component to the T-wave of the standard precordial tracings.

Figure 9, taken from a patient with marked hypertension and old anterior wall infarction, is of interest because of the appearance of a diphasic T in the 5 position and an inverted T in the 6 position, not found in the control series. Apparently, positive components contributed by positions 4, 3 and 2 have obscured T-wave inversion which became manifest only after the intermediate positions were blocked. Lead I shows inversion of T and more nearly resembles  $CF_5$  and  $CF_6$  of the experimental series than it does the standard curves. The similarity between Lead I and Lead  $CF_5$  is well known. At times, however, as in the case at hand, differences appear in these leads which can be clarified in the manner indicated.

## DISCUSSION

The findings reported emphasize the fact demonstrated so well by Wilson and his colleagues<sup>1</sup> that the precordial electrocardiogram is a composite in which the cardiac zone nearest the exploring electrode dominates the picture. However, the effects of more remote zones cannot be disregarded and the proper evaluation of any one precordial lead requires careful comparison with the others. In general, the influence of cardiac zones not in proximity with the exploring electrode has been neglected in the literature. We believe that this influence is frequently greater than has been generally appreciated and that it can be made more evident by the insulation of areas of the anterior chest wall. By this method we have attempted to distinguish QRS changes produced by the myocardium in proximity with the exploring electrode from those contributed by zones further to the right or left; and also to throw light on some apparent discrepancies between Leads I and  $CF_5$  which usually are much alike.

When the heart muscle nearest a given chest lead produces a negative deflection and adjacent zones produce positive deflections the actual curve we written may be a resultant of opposite effects. On the other hand, the underlying myocardium and adjacent zones may both contribute components in the same direction with an addition of effects. For example, *low* upright T-waves in  $CF_5$  and  $CF_6$  associated with *tall* upright T-waves in positions to the right may be just as good evidence of left ventricular strain as in-

version of T in  $CF_4$  and  $CF_5$  when T-waves to the right are low or inverted. It appears evident that one cannot interpret accurately the significance of the height and direction of any deflection in a precordial lead without determining its relation to comparable deflections in other areas.

A related problem concerns certain differences between Leads I and  $CF_5$  that occasionally appear, particularly in the direction of the T deflection. The fact that these leads usually present similar curves is well known. As illustrated in figure 9, T-wave inversion may at times be found in Lead I but not in  $CF_5$  because T-wave positivity contributed by zones to the right obscures the change in the chest lead. The inversion, however, becomes apparent when the interfering zones are insulated in the manner described.

### CONCLUSIONS

1. The insulation of certain areas of the anterior chest wall enables one to distinguish the electrical effects contributed by the myocardium nearest a particular chest wall position from those contributed by zones that are more remote.

2. The effects of remote zones are frequently greater than is generally appreciated.

3. These effects must be taken into account when precordial electrocardiograms are interpreted. Accurate analysis of the electrocardiographic picture in a particular precordial lead is impossible without careful comparison with the picture in adjacent leads.

4. Some apparent discrepancies between Leads I and  $CF_5$  are explained by the technic described. They result from the interference of relatively remote cardiac zones with the  $CF_5$  pattern.

The authors wish to express their appreciation to Chief Pharmacist's Mate E. D. Schwartz, USN, for his excellent technical assistance.

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## THE GOLDEN GATE OF MEDICINE\*

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MAY I begin with the bold hope that the almost effortless mastery of time and space which has brought you here has not imposed sophistication as the price of comfortable travel, nor robbed you of a pilgrim's vivid sensitiveness to stark and simple things. Unless, for a moment at least, you can give yourself to the realization of what this city of San Francisco has been and will always be, you will miss the significance as well as the fun of these meetings. That is why I hope you will abandon yourselves to the simplest things, dispense with all your reservations except perhaps the Pullman variety, and treat yourselves here to that rarest of American luxuries, contemplative reverie.

As one stares into a hearth fire the better to ruminate and reflect, let us think for a moment on the meaning of the Golden Gate. It made this city of San Francisco the goal of many an overland traveler and yet later a point of departure par excellence for those whose restless energies were not exhausted by the crossing of a continent. Fabulous as journey's end for the covered wagon, the Golden Gate redoubles its charm by being at the same time the gateway to the incredible variety of the Pacific Ocean. It was the spot where prairie schooners offloaded their tireless crews to real schooners and the Far West turned to the Far East in the paradox of the circle.

I hold to that word variety—the *variety* of the Pacific Ocean. For most of us have reached here the end of a known experience and find ourselves on the edge of a still greater ignorance. So I would find it simple and appropriate here at the Golden Gate to ask the question, "What next in Medicine?" It is a fitting time to look back over the road by which we have come, and forward to new ways of travel and new experiences. Because of the very simplicity of the comparison I want to talk about the Golden Gate of Medicine, for in so many ways in Medicine we seem to be at the end of one road and restlessly realizing it. Before we ask, "What next?," let us look back.

The past 75 years in medicine—our generation and that of our teachers—seem to me to have been influenced by an idea so general and pervasive that it escaped explicit attention. At the same time it has been so rewarding that, even unrecognized, it has dominated our activities. Even now it may seem elusive, for like magnetic attraction its effects are more easily pointed out than the force itself. This idea, or prevailing assumption, concerned not the description nor the treatment of disease, but its causation. This powerful idea involved the conviction, or at least the rapidly spreading

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assumption, that each disease has its own specific, single and sufficient cause. We cannot realize what a radical release this idea brought from the multiple yet simultaneous complexities of medieval thought—the tradition of the astrologers so nicely preserved for us in the very word *consider*, -*sidera*, the stars, and *con*, taken together.

In earlier centuries there had been speculation a-plenty. There had been descriptions of disease that cannot be improved upon today. There had been scattered fortuitous discoveries of remedies and effective methods of treatment. Then there gradually came a new approach. There is no particular year when such an assumption can be shown to have begun, nor any one event as its point of origin. But the discoveries of Pasteur and those that satisfied Koch's postulates, gave unexpected and yet convincing evidence that many diseases actually had specific causative agents. The immense success of these discoveries went further and focused most of the minds of the generation preceding ours on the problems of the cause of disease, and even quickened the suggestion that every disease must have its one unique, and uniformly effective cause. Now an idea that is both simple and immensely rewarding is certain to obtain increasing credence and eventual acceptance. Surely the concept of direct and unique causation is simple—indeed has proved deceptively simple. And yet what a harvest it reaped! Anthrax, hydrophobia, surgical sepsis, typhoid, diphtheria, tuberculosis, cholera, dysentery, childbed fever, tetanus, syphilis—what triumphs for almost a single generation! In the face of such a record it seems almost churlish to point out that this successful and all-pervading preoccupation with the specific causation of disease has produced anything in addition to the long desired mastery of many terrifying afflictions of mankind.

But the results have been more far-reaching than we realize. There has been a cataract of consequences, intellectual, ethical, social, economic, and educational, deriving from the effects of this idea that every disease has its own single and sufficient cause. Like a sudden and far-flung military advance it has called for extensive rearrangements along the entire line and in the services of supply. What are these changes?

First, by so much as you discover the causes of various diseases you begin the control of their incidence. Rationally and effectively to prevent disease was something startlingly new. The occurrence of disease had been for two thousand years considered a matter of chance or fate. We still exemplify that attitude when we say, "fortunately I have enjoyed good health all my life," but that phrase is more untrue now than we realize, for the diminished incidence of many a disease is now no longer a matter of luck but the result of the use of intelligence and effort and money. Epidemics that used to be excused as acts of God are now not excused as the results of the inactivity of man. In short, the incidence of many diseases has been moved from the area of chance to the area of choice. That is a vast change intellectually. Not only intellectually but also morally, for such a series of ac-

complishments leaves us with a new system of ethics to devise, somewhat as the perfection of the automobile has called for new traffic laws. As physicians we cannot evade a moral responsibility that goes with our newly acquired power. Having learned how disease comes about we find ourselves answerable for why it should occur at all. The oath of Hippocrates makes no reference to the physician's duty to prevent disease though we still solemnly intone it to graduating students as an admirable credo of our profession. Admirable but no longer adequate. No less paradoxically, the layman demands from us protection and prevention, but still is loath to pay for it because health still seems to him a matter of luck—and by definition nobody ever pays for good luck. So there are economic and social consequences as well as ethical. For mark you, the general public is beginning to realize that the well-trained doctor and his helpers can now deliver much that is as essential to life and comfort as food, clothing, and housing. But until people clearly and fully see that prevention and good care are as reasonable an expense of living as any other essential, we doctors shall drag on in the confusion of their thriftlessness, a confusion embittered by charges and countercharges of exploitation and evasiveness, of extortionate doctors' charges and patients' improvidence. The mastery of the specific causes of so many diseases has whetted the public's appetite for more. Our generation happens to live at a time when the cost of keeping well or getting well is increasing. The laity is only beginning a great transition from the easy indolence of regarding health as good luck, to the sterner realization that like food and housing, health can be had and must be budgeted and paid for.

One further fact will be recognized but only with harrowing delay; namely that the cost of training good doctors must be regarded as part of the cost of medical care, and like other forms of public education, is a reasonable and indeed a desirable charge upon the people's capacity to earn. Speaking of the people's capacity to earn, Americans spent for beer, wine and whiskey in 1946 eight billion seven hundred million dollars. I cannot escape the rueful reflection that we are just pikers when it comes to paying for medical care; perhaps the vulgar fact is that an alcoholic sense of well-being outbids being well. And I ought to add in justice to our Californian hosts that not all that eight billion seven hundred million was consumed in solitary drinking. Would that medical care had more of the exhilaration of conviviality! Perhaps the gregarious uproar of a medical congress dedicated to reducing illness is a sage substitute for the excitement of the alcoholic illusion of well-being.

The constant interest in causation that has prevailed during the past 75 years has produced another important effect. Scientific medicine is essentially an affair of the intellect. Consequently the attitude of two generations preoccupied with the cause of disease has been to regard the patient as presenting an intellectual puzzle. Let me repeat that this attitude was in many ways an immeasurable improvement upon the fumbling and bewildered empiricism of an earlier day. But to regard a malady as an intellectual

puzzle, provides the physician with such an absorbing task that he commits the commonest error of the scientific mind; he forgets, or overlooks, or ignores some important variables in the equation he is attempting to solve. Fascinated by formulations of disease which took beautifully precise account of the factors of bacteriology, immunology, cellular pathology, biochemistry, biophysics, and physiology, the clinician of the past two generations has taken at times too little account of the psychological factors—the patient as a person, the emotional aspects of his disorder, and the disorder of his emotions. Only because the pathological and physiological factors were so complicated, and yet so beautifully verifiable, did the clinician's attention often become almost blind to the psychological factors. Now a sleight of hand artist can divert our attention from one move he makes by making at the same instant another move that is spectacular and preoccupying. "Look at the dicky bird!" is in effect a blinding command. The astute boxer feints with his left to afford his right hand a mellow target. Of course Nature seldom feints deliberately to divert our attention. But, science provides us with instruments of entrancing accuracy, with oil-immersion lenses and potentiometers and spectrographs and x-rays, all of which are superbly efficient for seeing parts of the total picture. But even these remarkable instruments do not excuse us from the task of looking at the whole picture, or of deciding what part of the total picture is worth looking at. Quite to the contrary they make it seductively easy to look at something merely because it can be seen. Now even if an instrument of precision will automatically register, measure, and record a singularly active and colorful dicky bird, we may be giving all our attention to what is no better than a dicky bird for all its beautiful verifiability. If I may offer a facetious suggestion—why not add one more word to our medical dictionaries—*ornithographs*, a collective term to describe all the pictures of the dicky birds that deflect our attention from what is important, by substituting mere precision for true comprehensiveness of observation? Rapt attention to the part is the best guarantee that the whole will be ignored. Of course when the part explains the whole, attention to it is an elegant procedure, but when the part obscures the whole, preoccupation with the part exemplifies misleading exactitude, and science at its worst.

If the search for the direct and single and ultimate causes of disease is going to continue to be the characteristic and dominating preoccupation of medicine for the next two generations, then I would expect that over the same interval there will be a continuing neglect of chronic disease, of rehabilitation therapy, of the care of the patient as a person, of the psychological counterparts of disease, and of the art of medical education. Any of these aspects of medicine will be neglected where causes preoccupy the doctor's attention. And I would not be surprised at the restlessness of patients at being considered mere intellectual puzzles; nor at their nostalgic references to the old-style doctor who knew his patients (and, we may add, knew his patients better than he knew their organic diseases); nor at the growing

popularity of the nursing profession which is pre-occupied with treatment, not causes; nor at the acceptability of osteopaths and chiropractors who all but dispense with the problem of causation, and thus get down to the business of treatment with noticeable dispatch.

But of all the aspects of medicine which have been eclipsed by the absorbing and rewarding preoccupation of seeking the causes of diseases, the most elusive and most important of all is medical education; the educational aspect of medicine; the fact that medical education is not to be left as a random and casual set of initiatory rites and vigils for apprentices, but is a form of education and a most important form too. In the excitement of a flood of scientific discoveries we have ignored the truth that medical teachers have duties purely as teachers. We have acted as though a brilliant teacher had little to offer to the progress of medicine. We have ignored the fact that medical schools belong to still larger and more significant things called universities; that medical schools have problems as all schools have problems; and obligations as all schools have obligations. And we have almost forgotten that the deans should know, and care, as much about the technics and problems of teaching as the deans of other faculties.

There is not time to expand and explain in full each of these consequences, intellectual, ethical, economic, social and educational that derive from the preoccupation of medicine with the idea of causation. But the thesis that the dominating and most pervasive characteristic of medicine over these last 75 years has been this preoccupation with the cause of disease, explains and illuminates more of our past successes and more of our failures, more of our present strength and more of our current problems, than any other interpretation of our relatively recent past.

If this thesis be sound, then we can also understand why some of the efforts in the past four decades seemed, when they appeared, to be so new and interesting. We can see why these novel movements seemed to be refreshing statements of ignored or neglected fact, perhaps at variance to the preoccupation with cause, or at least complementary to it, and sometimes even challenging its dominance in medicine. Let me mention a few. Richard Cabot's espousal and development of Medical Social Service. Abraham Flexner's insistence that medical education must be dealt with as a form of education. The Commonwealth Fund's support of Child Guidance. Clifford Beer's creation of the Mental Hygiene Movement. Kretschmer, Pende and Draper as protagonists of Constitutional Medicine. Sir Thomas Lewis' championship of the importance of the natural history of disease. Francis Peabody's book on the "Care of the Patient." Canby Robinson's book, "The Patient as a Person." Howard Rusk's remarkable work in the field of rehabilitation medicine. And some more general trends: the steady rise of Public Health and Preventive Medicine, the unexpected development of Psychiatry, the establishment of a chair of Social Medicine at Oxford, the Goodenough report that recommends a reform of medical education in Great Britain in the direction of a larger emphasis on preventive medicine and

psychiatry; the report of the Committee on the Cost of Medical Care; and the current discussions of the distribution of medical care.

All these phenomena, it seems to me, are related and understandable, when we realize that the knowledge of cause has given our profession a measure of control over disease, which forces upon us new ethical standards, a new social status, and also reform in medical education, including the obligation to realize that we must reckon with more than single and unique causation when a patient comes to us. We have come to see that we must add more factors to our equations of illness—the factors, for example of emotion, or of heredity or of social and economic status of the patient. We must teach these factors, not tacitly admit them. We must further expand our thinking from simple and unique causation to include a knowledge of the laws of pure chance, of multiple causation and correlations.

I trust this does not seem too abstract and inapplicable to the present tasks that face American medicine, for if we are now at the Golden Gate and outward bound there are more urgent issues to deal with than a mere rationalization of our experience to date. They may not be as clear as the lessons of the past but they are new and pressing.

Among the present practical problems which affect, and might well concern the American College of Physicians, is a development of relatively recent years, the certification of specialists. If only to encourage discussion upon that theme, I will offer some critical comment from the viewpoint of one who believes in the rule that intense attention to one thing almost guarantees the neglect of another. It has been somewhat sarcastically observed that military staff-officers prepare for the next war by learning how to fight the last war better. If we devote the present vast energy and attention to raising the standard of performance in the application of what is already known, will American medicine be as alert and adaptable to change as it wisely should? In a world where in some ways change is the only constant, can we be wise to devote our attention away from the ability to change? Are we prepared to believe that nipping the laggards is the essence of leadership, or that enforcing minimal standards will ever discover or encourage originality and advance?

For a specialty to attempt to improve the performance of its members and give a better significance to its status, is admirable. But there is an implication in the method used that is not admirable. It is misleading and dangerous. The implication is that if any group of specialists decide to clean house and criticize themselves they should be given carte blanche and let alone. That is as false as to say that if you are virtuous according to your lights you are therefore moral, or that if each nation follows the dictates of its own conscience the result will be acceptable to all the others. For the fact is that if, after you have finished your own house cleaning, the neighbors still complain, then you may not be through after all. It seems important then to assert at the outset, that although a specialist society should be the first judge of its own excellence it never will be the ultimate arbiter. The

perhaps annoying fact is that the principle of absolute sovereignty won't work.

The specialist groups began on the basis of respect for the self-imposed standards of excellence of their mutually chosen members. Did they realize what a profoundly different thing it was to change over to examinations as the basis of recognizing excellence? Why is that a profoundly different system? Because admitting excellence is not the same as excluding incompetence, and because prophesying what may turn out to be excellent, is a far different thing from discovering what has been proved to be excellent. A board of examiners competent to examine on what it already knows, is neither disposed nor competent to examine on what it has yet to learn.

The chance of eventual recognition is a more encouraging circumstance for an original young specialist to deal with, than passing an examination set by those who can withhold approval of the new by insistent emphasis upon expert knowledge of the old. If the specialist groups had continued to elect their members on the basis of recognition of established competence, they would have avoided the serious danger they now run of being the unintentional partners of static and reactionary, albeit powerful and respectable, inertia or ignorance.

In plain truth our medical schools, still fumbling with the first four years of adequate medical education (which we all know is only about half of it), have let the specialists set up examinations in place of teaching, and now who is responsible? The certification boards write prescriptions for schools and hospitals that are neither solvent, nor staffed to provide what is prescribed; and then set examinations that do not and cannot establish the maturity or the competency that certification was intended to guarantee.

Anyone familiar with what the concours system has done to French medicine will be distressed to see American medicine putting its faith and its money on the capacity to pass written and oral examinations. The only competence so proved is the competence to pass an examination. Will obligatory and uniform experience (as soon after graduation as possible) followed by an examination, guarantee such excellence and maturity of judgment as to deserve permanent certification? Let us remember that the earlier the test the more immature the entrants.

If the greatest value for American medicine is to force up the general performance level of all specialists, by tending to the less fortunate, less trained and less gifted, there is much to be said for certification boards. However, another way to raise the general performance level is to exert vigilant and jealous control in behalf of excellence, variety, and freedom to go beyond our present knowledge. The very years you pre-empt for the uniform training for the boards are the most precious in the lives of those young men from whom progress is to come. You can see and I hope you can read, the price tag of the present emphasis upon specialty board examinations.

Another difficulty in the general field of according approval: certification on the basis of prescribed uniform experience, plus passing an examination is, very largely, an example of giving permanent approval for temporary performance. For in a series of specialties changing as rapidly and as continually as those of medicine, to have permanent approval based on temporary performance strikes my somewhat perverse sense of humor as ludicrous. You shaved day before yesterday and it was a nice job, but what about the situation at five today? Some states of grace are not permanent. The certification of a specialist, if his specialty is progressing, might well be limited to a period of 10 years and void thereafter unless validated by obviously excellent performance attested by his equals. We do something similar in obsolescent medical schools. Since I have known deans who hoped for a class B. status for their schools so they could wring money out of their legislatures for real improvements, I could hope that obsolescent specialists might wring concessions from their wives and their hospital boards, to refresh their knowledge and thus recapture the status they have lost.

If the examinations were designed and administered to find out what the candidate knows as a result of years of preparation, there would be some chance of recognizing his ability and accomplishments. But the tradition of examinations in this country is not to find out what a candidate knows, but whether he knows what his examiners know. And that, gentlemen, is a vastly different business in its effect on the candidate before and after the examination, and its effect on the self-assurance of the examiners. A field of knowledge is in a healthy state of cultivation when it is hard to find older men who know as much as the oncoming generation, or even think they do. In stagnant subjects the old always know more than the young and examinations make some sense, when used in moderation.

But there are further difficulties in certification by specialty boards. Their emphasis must be either on education, or upon the mere question of bestowal vs. withholding approval. Even if our medical schools and hospitals were not as far in the red as they are today, the preparation of candidates for certification as specialists would place upon our schools a burden they could not honestly carry without substantial outside help. If the schools, without any other financial support, were to charge what it costs to give the training which certification should require, their training would be so expensive that it would fall to pieces of its own financial weight. Or, worse still, such entrance to good standing as a specialist would increase the cost of becoming a specialist and so increase the excuses given for recovering the expenses later by high specialist fees. This would be unwise, for we are suffering quite enough from the notorious charges of some specialists and we may well be warned that the public is reluctant to give money for the gratuitous education of commercial minds. Would each specialist group tax themselves enough to supply and support enough training centers to renew their ranks? Unless this be feasible or some constant new source

of adequate support be found, the situation seems to me a rather heedless and confused tragi-comedy of hope and hypocrisy.

Perhaps you think the language strong. The intention of specialist certification is to raise the level of the performance of specialists. That seems admirable. But the most important characteristic of truly admirable people is not their credo but that they insist on forever reducing the gap between words and deeds, between the ideal and the actual, between credo and accomplishment. The specialist societies assumed that ever increasing amounts of money would be found to strengthen and enlarge the facilities and the personnel required: but the depression and four years of war came instead. Research experience is not encouraged: the young men usually will jump only the stipulated hurdles. The specialists cannot pay the piper but they have called the tunes, taking to themselves the freedom, and leaving to the schools and hospitals the responsibility.

There is some evidence that the press of candidates for certification has prevented some boards from considering what their long-term policies should be. The seriousness of the situation becomes more apparent when one realizes that in some fields the numbers applying for certification are so large that the only way of reducing the examination to manageable proportions is by the true-false system of examination questions. Sometimes there is too little time to test the clinical competence of a candidate. The power the specialty boards possess is now increased to an uncontrollable degree because hospital boards and government services have discovered the comfort of passing the buck by letting certification be the basis of appointment, and in some cases of salary status. It seems rather naive for anyone to be surprised that lay trustees of hospitals or government agencies are putting a cash value on specialty board certification. Where do you suppose they could have gotten the idea that there is already an "aristocracy" in medicine, if not from the "aristocrats?"

If the specialists would stop to think of how valuable to their welfare is an abundance of well-trained general practitioners, they might pause before giving their unhesitating support to a development that discourages and deprecates general practitioners.

I am going to make a statement about subordinate specialties—so first let me say what I mean by subordinate specialties. They are those specialties whose practice is dangerous without a sound knowledge of medicine and surgery. Putting money and prestige value on certification will certainly result in this: the subordinate specialties will claim independence of internal medicine or surgery. Now we all could save quite a lot of time and bother for ourselves by letting the subordinate specialties disregard the advantages of broad training, but the price tag of this neglect will be outraged public opinion, slow in developing, but strong and reckless in its later stages, and scornful of specialists narrowly trained.

We would do well to regard the present state of specialty certification as a poor substitute for sound thinking and further realistic action. It is,



in part, symptomatic of our outmoded system of state licensure. If the problem is to keep the specialties clean of pretense and incompetence, the Council on Education of the American Medical Association should pass upon the facilities for the teaching-hospital training of candidates, at least as closely as it passes on our medical schools. At present the Council and the Specialty Boards are not adequately inspecting or influencing the quality of residency training given in hospitals as part of the training of specialists. How will they judge the product of their neglect? The National Board of Examiners should administer the examinations but only to candidates who have completed a thorough preparation to the satisfaction of the teachers in schools and teaching hospitals approved by the Council on Education. This would focus attention where it belongs, on the educational aspects of medical education, and not on the self-determined exclusiveness of a series of well-meaning but narrow professional groups.

The National Board could very wisely use the specialists' knowledge and desire to keep their ranks free of incompetents and imposters. The specialty board certification, if it is inescapable, should be continued, but the National Board should have the final authority, if need be, to override a position taken by a specialty board. Why? Because history shows that cliques and factions within a specialty are less dangerous if they must explain their views to other judges than their own prejudices. What would a self-regulating specialty board in surgery have done with the application of young Lister for certification? Can we learn nothing from history? Can we not foresee and forestall the dangers of specialty board certification, where so much power is held narrowly?

On the other hand if the purpose of the specialty boards were to distinguish and reward the merit and accomplishments of specialists recognized as not merely competent, but excellent leaders, then examinations should be dispensed with, as they were at the beginning. When you force Board certification upon virtually all possible candidates by the devices of limiting society memberships, hospital appointments, and appointment or promotion in government service to holders of certificates, you include among your triumphs many young men who would have reached distinction without Board examinations. Indeed they would have succeeded in ways more varied, original and productive of fresh advances, than via the uniformity your best judgment imposes. And while facilitating the entry of the immature who happen to be ambitious, you will forego the membership of more mature men who happen to be as interested in their work as they are in their careers.

If the level of the practice in certain specialties has improved, is it any more likely that certification boards did it, than that the general level of wealth and education was the greater factor in play? Was the patient already mending when the new treatment was begun? Granted that the preparation required for certification is one method by which a doctor can

claim the status of a specialist, it has not been and it is not the only way. Why then reinforce it so heavily with prestige and cash value?

But one really important fact besides the wish to protect the public ought to be realized and utilized: at present the first 10 years of an American doctor's professional life are apt to contain too many hours of waiting to use the skills and knowledge he has acquired. It is an inexcusable waste of the strength, the competence, and the ambition of thousands of young men, able and eager for a better use of their time. That realization, which is not clannish or exclusive, offers the best point of departure in measures to improve the performance of specialists.

It takes 10 years to make a truly competent and responsible doctor. Would it not be useful to back off and regard that 10 year period for what it is—an essential unity? Instead we look at it piecemeal. We have put the first four years in care of the universities and taken a good deal of satisfaction in getting rid of the proprietary schools and the purely professional control they gave to medical education. Examinations for the license to practice helped to strengthen the assumption that four years were enough. But the stubborn fact remained that four years were not enough. Indeed it became increasingly true that four years were not enough. Minnesota with admirable realism insisted on the intern year. Attention began to focus on internships and residencies, but very few medical schools were in a position to assume explicit and extensive responsibility or control of the training given their graduates. The control drifted. And with the rapid rise of board certification, control is drifting still further away from the schools and the teachers of medicine, into the hands of the practitioners via the specialty boards. The task of the next two decades is to put ten-tenths of medical education, not four-tenths, where it belongs.

I have offered these comments because they touch upon something that is tangible and concrete, and because the defects of specialists' certification illustrate a danger to the most precious element in any profession. What is the quint-essential element? The biological commonplace, that when a cell becomes highly differentiated it loses its power of regeneration illustrates my belief that the demands of a highly specialized and exclusive activity endanger the most precious element in any profession—namely its capacity for change and growth, for regeneration and continuity. A powerful and efficient eunuch is nearer to death itself than a corpse with six sons and daughters as pallbearers. The different experiments of Nature show that the infinite variety of what Muller calls "the dance of the chromosomes" is a more tenacious because it is a more variable way of continuing life than mere cellular fission. Freedom is more than a pleasure principle: it is a guarantee of vitality and survival through variety. Every tendency in our profession, especially every trend that seeks to strengthen its position by means of standardization, obligatory uniformity and unvarying acceptance deserves to be challenged as a threat to variety and survival.

At the beginning of this paper I traced the consequences of a dominant and wonderfully rewarding preoccupation with the view that every disease has a single and sufficient causative agent, because I believe with Vannevar Bush that science is an unending frontier, and because even as scientific a concept as unique causation fails to supply the variety that medicine must encourage if we are to go on from here.

We must fend for the future of medicine by protecting its freedom to change and grow. There is no surer way of seeing the potentialities of a given subject than to examine its relation to all that is *not* it, but around it. It is an extension, not a negation, of clinical medicine to explore its own outside relations; the relations, for example, of somatic and organic disease to the findings of psychologists, sociologists, and geneticists. Not only is there an interior milieu for the body, but socially an exterior, and genetically an anterior, milieu. So frequently have we contrasted the individual with the mass that the word "individual" has come to have the connotation of isolation or separation. But the essence of individuality is the uniqueness of the individual's ties to his environment, and the indivisible cohesion or inseparability of these ties. Surely that idea alone points to a gateway outward on uncharted seas and to a variety of new lands.

But there would be an ironical humor if one were to argue for variety and freedom by attempting to list the opportunities. Freedom transcends lists and smiles at outlines. As the Arab chief remarked to Gertrude Bell, "Madam, may I remind you that liberty is never given—it is always taken."

One can, however, speak of preparations for a voyage even when destinations are merely to be presumed, as did Columbus when he left the western shores of Europe. Let us hope that medicine will take the appropriate courses to reach many more than the destinations already presumed—psychosomatic medicine, industrial medicine, social medicine, genetic medicine, rehabilitation, the natural history of disease, growth and aging. So please bear with me as a person given, and perhaps too much given, to abstract thinking, if I offer two hints for those embarking for new destinations in medicine.

One is that we all should make definite efforts to encourage more recording of unexplained phenomena. In comparing American medicine with that in some other countries I have had the impression that we lack a certain kind of scientific candor in that we fail to encourage the observer of inexplicable phenomena. We seem averse to seeing a naked uninvited fact at our feasts of reason. A fact, we seem to feel, should be clothed in at least an hypothesis, or better still in the uniform of experimental confirmation. So the price of our fear of the raw is a dull habituation to the conventional. I make this plea because it is hard enough for a young and original observer even to see what he cannot explain, without having the additional difficulty of formal discouragement from editors and audiences if he attempts to describe and record the obstinate beauty of an unacknowledged, unexplained fact.

The other counsel we should all offer to those setting out for continents unknown, or at least not as yet too much explored, is that they should attach more importance to the mental processes by which they interpret the relationships between the phenomena they observe. There could be rules of evidence in medicine as in law, and our medical schools would demand more rigorous thinking and more critical reading if they were to emulate the better law schools in training students to make the correct inferences from observed events: a course called Evidence. The incapacity to think straight flourishes like a weed in the virgin soil of our rank neglect of the meaning and use of words. This tare is watered by an ignorance of the laws of probability and sunned by callow personal ambitions. Almost never uprooted by a critic who distinguishes between chance, correlation, and the three main types of cause, predisposing, precipitating and perpetuating, this weed—the incapacity to reason—overruns our medical literature and chokes out that rare but almost infinitely valuable plant, whose fruit would nourish us—sound reasoning. With publication so important a means of securing recognition, and with communication so important a tool for the progress of medicine, there is both urgency and importance in fostering a much more discriminating insistence on sound thinking and clear expression in our professional literature. I would not be discouraged at the depressing style of medical writers if such language led them to conclusions that were valid and well knit. And I would not be apprehensive if the journals that carry articles containing any reasoning at all were to appear but twice a year, provided conclusive reasoning was the characteristic of every article printed. But I cannot see satisfactory progress for medicine until we pay explicit and forceful attention to what is proof, what is evidence, in contrast to what is mere linked softness long drawn out.

But the essence of my plea to you has not been hints on procedure, nor criticism of one handicap from which we may suffer increasingly, nor exhortations as to what new goals medicine should set itself. I have suggested that we have been greatly preoccupied during the last two generations with the idea that each disease has its own single, sufficient and specific cause, perhaps so much preoccupied that Medicine must now look to a wider horizon of interests in order to find freedom, and variety for survival. To simple precision of observation we must vigilantly add comprehensiveness of observation, and from familiarity with only simple causation we must advance to a greater complexity and rigorousness of thought. We have crossed, but not fully occupied, an area of pathology and physiology that is continental in its magnitude and variety. In ways that make the comparison not too grandiose we have come to the edge of a continent, to a Golden Gate. Whitehead comparing our times with other periods has said, "This is the largest epoch in human history." Our hope must be that Medicine—which, to include all its branches, we might call Great Medicine—that Great Medicine will go on and out to meet change, to seek variety, and with greater vigilance to purchase and deserve a greater freedom.

# CASE REPORTS

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## PARATHYROID CARCINOMA ASSOCIATED WITH ACUTE PARATHYROID INTOXICATION \*

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ACUTE parathyroid intoxication in man has been reported but 10 times<sup>1, 2, 3, 4, 5, 6</sup> and, except in one instance in which the intoxication was caused by the injection of parathormone,<sup>2</sup> has always terminated fatally. The case to be reported appears to be the first in which carcinoma of the parathyroid gland was associated with acute parathyroid poisoning. This case is of particular interest in that the patient survived one episode of acute intoxication which was terminated by surgical removal of the gland, only to succumb to a recurrence of the same condition six years later. The purpose of this report is to present a case of carcinoma of the parathyroid, to describe the clinical and pathological aspects of acute parathyroid intoxication and to emphasize the importance of prompt surgical intervention.

### CASE REPORT

M. O'G., a 59 year old spinster, entered the Peter Bent Brigham Hospital for the third and final time April 26, 1946, complaining of nausea and vomiting of nine months' duration. Her present illness apparently began in 1926 with the onset of pain in the arms, legs, back and ribs. Examination in the Outpatient Department in 1928 revealed obvious stooping and shortening of the body. Roentgen-rays of the spine showed a diffuse atrophy and collapse of several dorsal vertebrae with coarse trabeculation of the pelvic bones. The serum calcium level was found to be 15 mg. per 100 c.c., and a diagnosis of hyperparathyroidism was made. The patient refused further study at this time, and was placed on calcium lactate, 25 grains daily by mouth, and cod liver oil. In 1932 a urinalysis showed a specific gravity of 1.030 with no albumin and a normal sediment. She continued to feel fairly well until 1938 when she fractured her right elbow in a fall downstairs. While recovering from this accident she experienced her first attack of nausea and vomiting which subsided spontaneously in about three weeks. The fracture healed slowly and the patient remained comparatively well until May, 1940, when nausea and vomiting recurred. These became progressively more severe during the next three months until she was unable to retain even water. The vomiting was unassociated with meals and there was no complaint of abdominal pain. She also noted polyuria, increased thirst, and weight loss of 28 pounds in the five months prior to admission to the Medical Service, on October 1, 1940.

The past history was of interest in that the patient had had a popliteal angioma removed in 1899 with subsequent paralysis of the left peroneal nerve and atrophy of the left lower leg. Ten years later she had an operation for a deformity of her right foot. In 1909 she spent three months in a sanatorium following a pulmonary hemor-

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rhage. The diagnosis of tuberculosis was never proved and she was discharged cured. Except for a deficiency of milk, her dietary history seemed adequate. In 1920, she was incapacitated for four months with swelling and pain in her joints which subsided without recurrence.

*Physical Examination.* At the time of admission in 1940, the temperature was 98.6° F., the pulse 78, the respirations 20, and the blood pressure 160 mm. Hg systolic and 88 mm. diastolic. The patient was moderately dehydrated. There was scoliosis and kyphosis of the dorsal spine, limitation of extension of the right arm, atrophy of the left leg, and ankylosis of the left ankle. Several hard masses were palpated in the muscle just above the left popliteal space. A hard, marble-sized mass was palpated in the lower pole of the thyroid. The reflexes were hyperactive. The remainder of the physical examination was negative.

*Laboratory Data.* The urine had a specific gravity of 1.010 and contained 1+ albumin and numerous red and white cells. The Sulkowicz test was 4+. The hemoglobin was 95 per cent and red blood cell count 4,860,000 per cu. mm. These values fell to 68 per cent and 3,800,000 per cu. mm. respectively on restoration of a positive fluid balance. The serum calcium concentration was 22.4 mg. per 100 c.c. This is one of the highest values yet reported in man and approaches the maximum levels reported by Cantarow, Stewart, and Housel<sup>7</sup> in dogs fatally poisoned with parathormone. The serum concentration of phosphorus was 3.4 mg., of phosphatase 10.6 Bodansky units and of protein 7.7 gm. per 100 c.c. The serum chloride level after hydration was 77 m. eq. per liter. A urea clearance test averaged 20 per cent of normal and the phenolsulfonphthalein excretion was markedly delayed, with a total of 25 per cent in two hours. The blood non-protein nitrogen ranged from 31 to 61 mg. per 100 c.c. Roentgen-rays showed extreme generalized osteoporosis, soft tissue calcification of the left hamstrings and definite cystic areas in the distal end of the right humerus. No renal calculi were seen and there was no roentgenographic evidence of intrarenal calcification. Cystoscopic examination revealed a chronic cystitis and evidence of bilateral chronic pyelonephritis.

*Hospital Course.* The patient continued to have intractable vomiting, and on the fourteenth hospital day, the diagnosis of hyperparathyroidism having been established beyond reasonable doubt, the region of the left lobe of the thyroid was explored under local anesthesia. Two masses, 2 by 2.5 and 3 by 3.5 cm., were found adherent to the thyroid. To expose the deeper of the two masses, it was necessary to remove the left lobe of the thyroid. There were adhesions around this accessory tumor; it was separated with difficulty from the esophagus, and the left recurrent laryngeal nerve which ran through its substance had to be sacrificed.

Postoperatively the patient did well. The vomiting promptly ceased and the bone pain which had been a consistent part of the picture gradually diminished. The serum calcium level fell to 13.0 mg. per 100 c.c. in 48 hours and to 11.4 mg. per 100 c.c. the fourth postoperative day, at which time the serum phosphorus level was 1.24 mg. per 100 c.c. and the Sulkowicz test on the urine was negative. At no time was there any sign of tetany. She was discharged on the tenth postoperative day on a diet high in calcium, phosphorus, and protein.

Grossly the specimen removed at operation consisted of an irregularly shaped tumor and a portion of normal thyroid. The tumor weighed 5.8 gm. It was composed of a solid mass of soft, delicately lobulated, pinkish-gray tissue and several cysts. One cyst, which measured 1.9 cm. in diameter, had a thick fibrous wall and there were several papillary projections of tumor into its cavity. There were several small, thin-walled cysts which measured less than 3 mm. each.

The specimen was fixed in acetic Zenker's solution, formol Zenker's formalin, and absolute alcohol, and stained with eosin and methylene blue, hematoxylin and eosin, phosphotungstic acid and hematoxylin, Mallory's aniline blue, Best's carmine, and Weigert's elastic tissue stains.

Microscopically the tumor was composed of round and oval, compact masses of cells, separated by interlacing columns of collagenous connective tissue which branched into fine anastomosing strands, the whole having a lobulated appearance (figure 1). There were many thick-walled vessels in the larger septa with a rich capillary network in the large masses of tumor cells. The tumor mass was surrounded by a fairly thin capsule composed of loose connective tissue. The tumor had invaded the

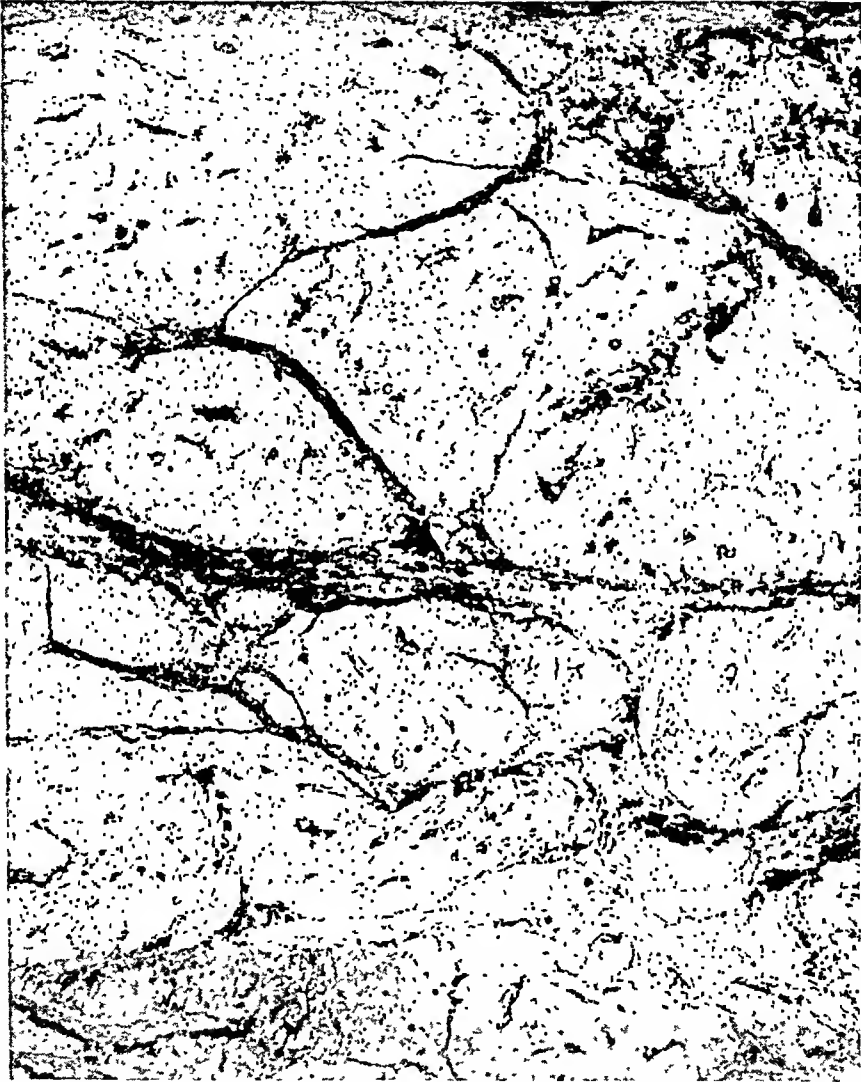


FIG. 1. The parathyroid tumor removed at operation. Note the lobular character. Magnified 43 times. Mallory's aniline blue.

capsule at several points. The thick cyst wall was composed of laminated, acellular bundles of collagenous connective tissue. Small papillary processes projected from the cyst wall into the lumen. These were formed of loose connective tissue cores and covered with epithelial cells.

The masses of compact tumor cells showed a striking perithelial arrangement. In several instances there was also a suggestion of palisading of the cells along the septa. In no place were acini apparent. The tumor cells were in direct contact with

many of the capillaries. The tumor was seen invading veins, capillaries, and lymphatics.

The major portion of the tumor consisted of large, polyhedral cells with distinct basophilic cell borders (figure 2). There was abundant, finely granular, faintly eosinophilic cytoplasm. The cytoplasm of some of the cells was pale and a few cells showed clear halos about the nuclei. The Best's carmine stain demonstrated a small amount of glycogen in minute droplets in many of the cells. The nuclei were ec-



FIG. 2. Higher power of surgical specimen. Magnified 480 times; eosin-methylene blue.

centric, vesicular and contained varying amounts of chromatin. The nuclear membranes were prominent and basophilic. In most of the nuclei the chromatin was finely granular and evenly distributed. There were usually two to three dark nucleoli. Occasionally the nuclei were pyknotic but no mitotic figures were seen.

The patient was followed in the Outpatient Department for the next four and one-half years. She was treated with calcium gluconate, 4 gm. daily and improved markedly both subjectively and objectively for three years. She felt well enough to



work in the garden, most of her bone pain disappeared, and she gained 35 pounds. During this time there were no urinary symptoms. The blood pressure varied from 148 to 164 mm. Hg systolic and 74 to 100 mm. Hg diastolic. Roentgen-rays taken during this period showed progressive evidence of new bone formation.\* The calcium and phosphorus levels were as follows: in 1941, the serum calcium concentration was 10.0, and the phosphorus, 2.4 mg. per 100 c.c. In the latter part of 1942, the calcium level was recorded as 11.8, the phosphorus was 0.9 mg. per 100 c.c., and the patient became more easily fatigued. In May of 1943, the serum calcium concentration was 13.0 and the phosphorus 2.48 mg. per 100 c.c. At this time the patient complained of lack of energy and pain in the right hip, and from this time on there was failing vision and gradual loss of weight. By 1945 she was incapacitated by bone and joint pain and had lost 22 pounds. The serum calcium was 16.8 and the phosphorus was 3.1 mg. per 100 c.c.

The patient failed to return for follow-up and was not seen until April of 1946 when she was admitted to the hospital because of persistent nausea and vomiting of nine months' duration. During this time, 16 days was the longest period that she had gone without vomiting. She had had constant bone pain similar to the pain she had experienced prior to her first operation. In November 1945, she had fractured her right humerus just above the elbow as she raised her arm to grasp a banister. This was the first fracture that she had suffered since her operation. Three weeks before entry the patient thought she had heard several ribs crack while coughing. This was followed by chest pain which was aggravated by breathing.

*Physical Examination.* The temperature was 99.6° F., the pulse 68, the respirations 24, and the blood pressure 120 mm. Hg systolic and 50 mm. diastolic. The physical examination at this time showed extreme dehydration and lethargy. She was unable to sit up in bed because of pain in all the extremities. There was generalized bone tenderness and a non-united fracture of the right humerus. The eye-grounds showed only minimal arteriosclerotic changes. The heart and lungs were essentially normal. No masses were palpable in the neck.

*Laboratory Data.* The urine attained a maximum specific gravity of 1.012 after the injection of 1 c.c. of pituitrin. It contained 2+ albumin and numerous white cells. The Hinton test was negative. The hemoglobin on admission was 12.8 gm. per 100 c.c., falling to 8.4 gm. per 100 c.c. after the patient had become hydrated. The hematocrit was 34 per cent at the time of admission. The white count varied between 2700 and 8000 with a normal differential. The blood urea nitrogen level was 44 mg. per 100 c.c. and plasma protein concentration 6.1 gm. per 100 c.c. The fasting blood sugar level was 111, serum cholesterol 316, calcium 13.8, and phosphorus 4.3 mg. per 100 c.c. The serum phosphatase was 25 Bodanski units. Two phenolsulfonphthalein tests averaged 8 per cent excretion after two hours and the urea clearance was 10.5 per cent of normal. Roentgen-rays revealed the characteristic bone changes of hyperparathyroidism, even more pronounced than before the patient's operation in 1940. A 24 hour urinary calcium excretion was 382 mg. at a time when the patient's calcium intake had been negligible for several days.

The changes in serum electrolytes are shown graphically in figure 3. The admission serum level of chloride was 114 m. eq. per liter and the serum carbon dioxide combining power was 12.7 mM. per liter. During the next three days, following the parenteral administration of glucose, saline and sodium bicarbonate, the serum carbon dioxide combining power rose to 17 mM. per liter, but the serum chloride concentration fell to 81 m. eq. per liter. More intensive therapy with intravenous saline

\* We have avoided the terms decalcification and recalcification because of the erroneous impression these terms convey. Enchondral bone is formed by the deposition of bone matrix (osteoid) which is subsequently calcified. When resorption takes place, the bone matrix as well as the mineral salts are removed. Therefore, the bone matrix must again be laid down before recalcification can take place.

and sodium lactate succeeded in restoring a normal serum chloride level although the carbon dioxide combining power never reached normal.

*Hospital Course.* In spite of continued efforts to restore and maintain a normal electrolyte balance in order to prepare the patient for operation, she continued to have intractable vomiting. For the first 10 days she ran an irregular fever as high as 103° F. Thereafter, her temperature remained below 100° F. The blood urea nitrogen concentration remained between 35 and 45 mg. per 100 c.c. throughout her

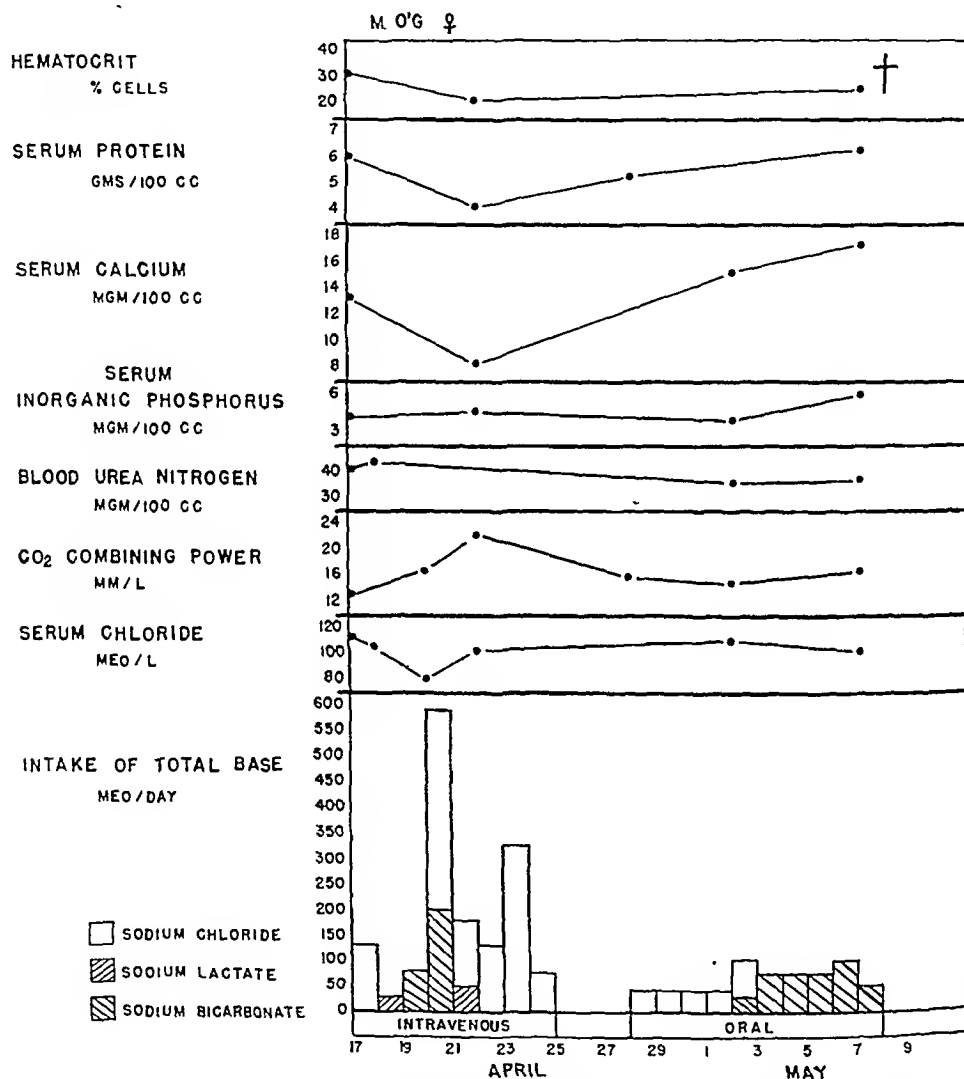


FIG. 3. Terminal changes in hematocrit, serum protein, urea and electrolytes in patient M. O'G.

hospital stay. The hematocrit fell to 23 per cent and continued at that level. The serum protein level after falling to 4.2 during the initial period of hydration gradually rose to 6.4 gm. per 100 c.c. The serum level of calcium rose from 13.8 to 17.6 and of phosphorus from 4.2 to 6.0 mg. per c.c. during the third week following admission. On the twenty-third hospital day the patient's general condition seemed unchanged. During the night, however, her pulse suddenly became imperceptible, she lost consciousness, took a few deep respirations and died.

*Autopsy Findings.* The body was that of a well developed, fairly well nourished, white female which measured 141 cm. in length. The left foot was smaller than the right with a slight inversion deformity. There was a right dorsal, left cervical scoliosis. There was a very large, bony hard mass behind the left knee just above the popliteal space. This was incorporated in the muscle tissue. It weighed 150 gm. and consisted largely of bone. There was a hard mass attached to the bone in the



FIG 4. Pulmonary artery showing medial calcification. Magnified 100 times.  
Von Kossa's silver nitrate.

supracondylar region of the right elbow. The peripheral vessels were calcified and tortuous.

The body cavities showed no abnormalities. The heart was normal except for calcification of the coronary arteries. The lungs showed edema. The spleen weighed 320 gm. There were several cavernous hemangiomas and a recent infarct. The gastrointestinal tract, pancreas and liver were normal. The gall-bladder contained no stones but showed the white reticulated pattern of cholesterosis.

The kidneys weighed 120 and 130 gm. The capsules were only slightly adherent. The external surfaces were coarsely granular with small, shallow, finely granular scars. Longitudinal sections of both kidneys showed the cortex and medulla of each to be well demarcated. The cortices averaged 0.5 cm. in width. The tubular striations were accentuated by small deposits of calcium. The vessel walls were thickened.

The adrenals weighed 11 and 14 gm., but were not remarkable. There was a cervical polyp and several leiomyomas of the uterus and some of these were calcified.

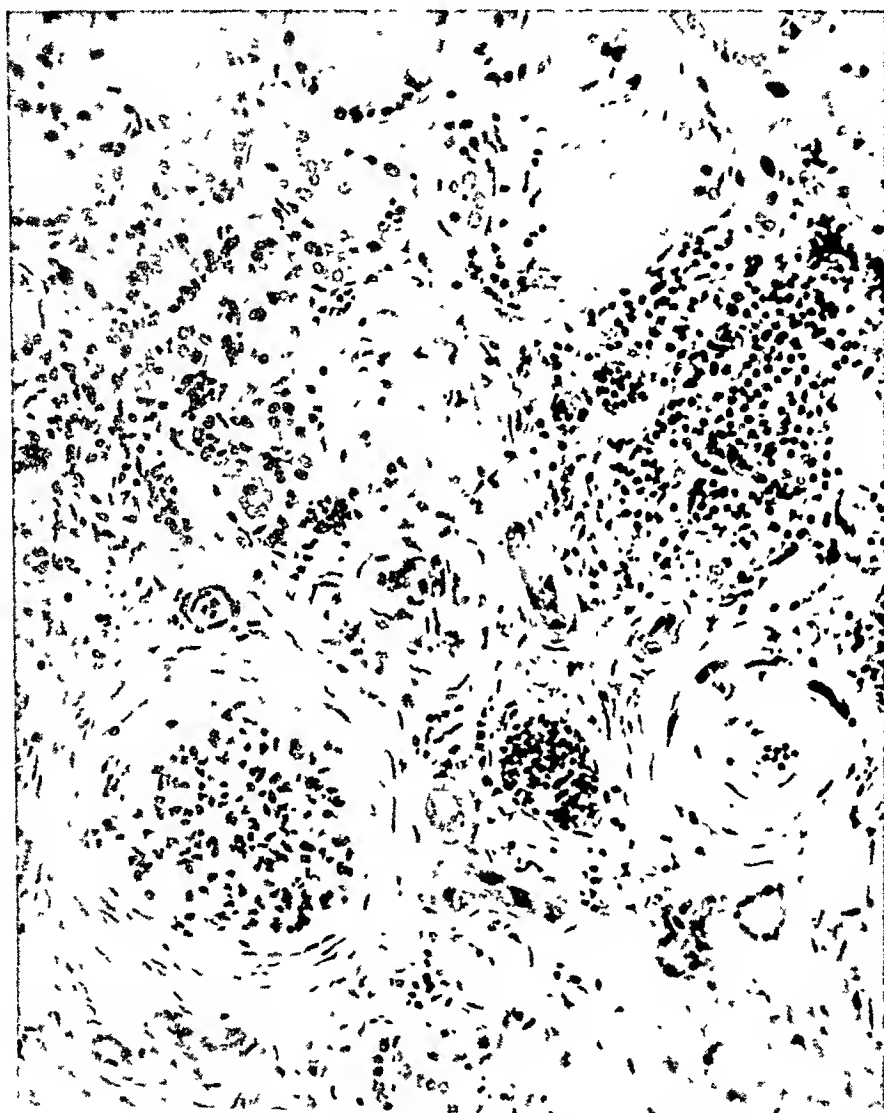


FIG. 5. A section of the cortex of the kidney showing typical chronic changes. Magnified 220 times. Eosin-methylene-blue.

The ovaries were atrophic. The aorta was markedly atheromatous and calcified, especially distal to the renal arteries. The vena cava and tributaries were unremarkable.

The left lobe of the thyroid was not present. The right lobe weighed 14.5 gm. and appeared normal. There was a firm mass of tissue concealed beneath the left sternocleidomastoid muscle. This was adherent to the posterolateral aspect of the larynx and esophagus. The mass was egg-shaped and measured 3.5 by 2.5 by 2.5 cm.

It weighed 10.0 gm. and was covered by a thin, shaggy, fibrous capsule. On cross-section, it was gray and lobulated and had a dense fibrous stroma. Normal parathyroid glands were not located.

The skeletal system showed generalized fragility and softening. The cortex was markedly thinned and the medulla was soft and mushy. Examination of the brain was negative.



FIG. 6 A section of kidney showing calcification in and about the tubules. Magnified 240 times. Hematoxylin and eosin.

*Microscopic Examination.* Routine sections were fixed in acetic Zenker's and stained with eosin-methylene-blue. Additional blocks were stored in formalin and special stains done when indicated.

Sections of the heart showed the epicardium and endocardium to be negative. There were areas of fibrosis in the myocardium which were focal in some areas and diffuse in other areas. There were deposits of calcium in the media of some of the medium sized arteries. There was hyaline intimal thickening of the larger coronary arteries.

The sections of the lungs showed considerable edema. The striking feature was the rings of calcium in the walls of the arteries of varying sizes (figure 4). Large deposits of calcium were seen throughout the media. A few polymorphonuclear leukocytes and lymphocytes were found about some of the calcium deposits. Some of the larger arteries showed small areas of fibrosis about them. The vessels also showed hyaline intimal thickening. There was no calcium in the bronchial walls.

The capsule, trabeculae, and Malpighian bodies of the spleen were not remarkable. There were many polymorphonuclear leukocytes scattered in the red pulp. One area, several millimeters in diameter, was infarcted. A fresh thrombus was seen in a medium sized artery. In the sections two cavernous hemangiomas were seen. The

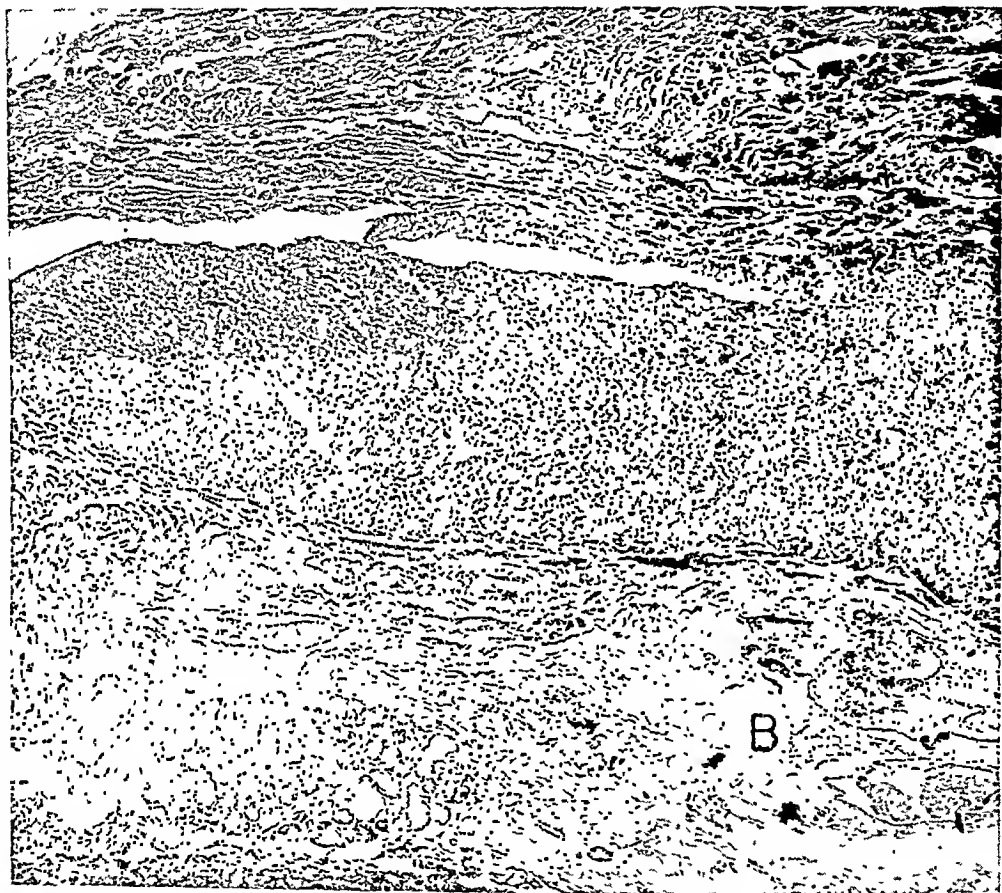


FIG. 7. A. Tongue of tumor invading esophageal muscle. B. Tumor in veins. Magnified 43 times. Eosin-methylene-blue.

pancreatic acini and islets of Langerhans appeared normal. There was a small amount of squamous metaplasia of the ductile epithelium and a few dilated ducts. The vessels showed hyaline intimal thickening but no calcification. The liver was normal. The tips of some of the mucosal folds of the gall-bladder were swollen with deposits of cholesterol. There were a few small collections of lymphocytes in the submucosa.

Sections of kidney were stained with eosin-methylene-blue, hematoxylin and eosin, phosphotungstic acid-hematoxylin, Weigert's elastic tissue stain and von Kossa's silver nitrate stain for calcium. The striking feature was the diffuse fibrosis of the interstitial tissue. This was seen surrounding all of the tubules and glomeruli

(figure 5). There was a diffuse infiltration of chronic inflammatory cells. Deposits of calcium were present in the lumina of the proximal convoluted tubules and, in some instances, were present in the interstitial tissue beneath the tubular epithelium (figure 6). No areas of necrosis were noted. Many of the tubules were dilated and showed degenerated epithelium. Most of the glomeruli showed pericapsular fibrosis and many of the glomerular tufts were hyalinized. There was hyaline intimal

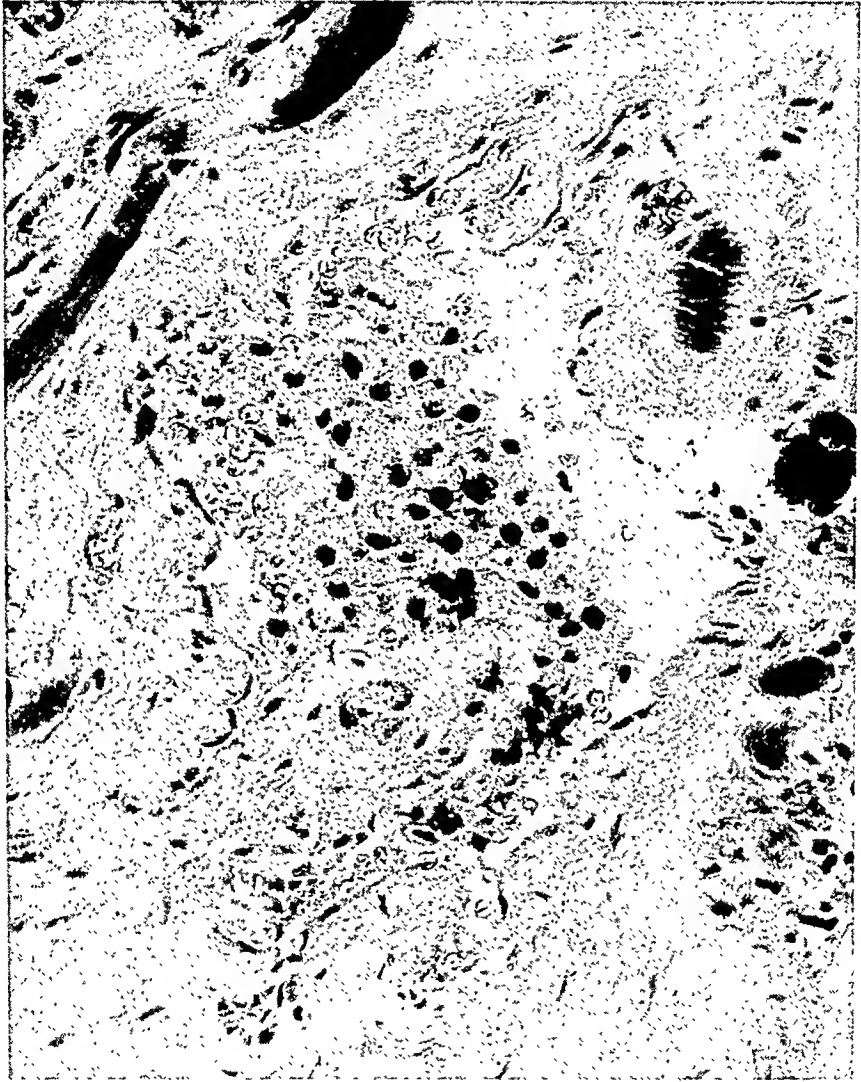


FIG. 8. Vein at periphery of tumor showing invasion by tumor. Note muscle bundles about vein. Magnified 300 times. Eosin-methylene-blue.

thickening and reduplication of the elastica of the larger vessels. Many lymphocytes were present beneath the epithelium of the calices.

The endometrium was not remarkable. Some of the vessels of the myometrium had deposits of calcium in their walls. The section of one leiomyoma showed large areas of bone. There was a cervical polyp.

Eight blocks of the parathyroid tumor were fixed in acetic Zenker's formalin, and absolute alcohol, and embedded in paraffin. The sections were stained with eosin-

methylene-blue, hematoxylin-eosin, Weigert's elastic tissue stain, Mallory's aniline blue, phosphotungstic acid-hematoxylin and Best's carmine. The general lobulated architecture found in the surgical specimen was preserved in the tumor at autopsy. Interlacing bands of thick collagenous connective tissue enclosed islands of tumor cells. The tumor cells had lost the perithelial arrangement which was so striking in the surgical specimen. There were several large areas of necrosis and many collections of lymphocytes scattered throughout the stroma.

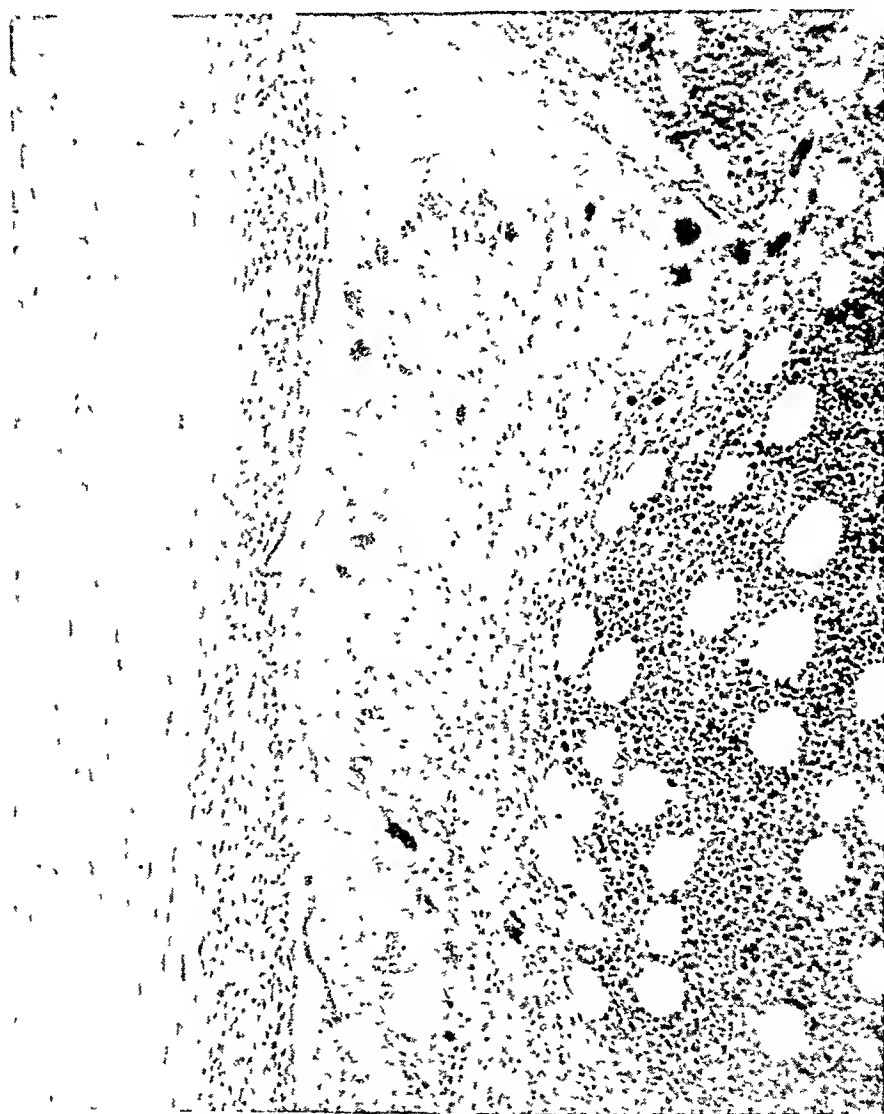


FIG. 9. Vertebra showing osteitis fibrosis cystica generalisata. Magnified 118 times. Hematoxylin and eosin.

The cytology of the two specimens was difficult to compare because of the different lengths of time intervening before fixation. The cells in the autopsy specimen were large and polyhedral. There was abundant granular eosinophilic cytoplasm. No cells with clear cytoplasm were seen. Best's carmine stains showed no appreciable amount of glycogen. The nuclei were hyperchromatic; however, no mitotic figures were seen.



The tumor was found deep in the esophageal muscle close to the submucous glands (figure 7). Masses of cells were demonstrated in many veins and lymphatics (figure 8). These almost occluded the lumina and conformed to the shape of the vessel wall.

Paraffin and celloidin blocks of vertebra, ribs, femur, sternum, skull and ilium were prepared. These were stained with eosin-methylene-blue, hematoxylin and eosin, phosphotungstic-hematoxylin, and Mallory's aniline blue (figure 9). The cortical bone was much thinner than usual. The Haversian canals were so increased in size that there were only thin columns of bone between them. There were large multinucleated osteoclasts seen adjacent to the thinned cortex and close by orderly arranged osteoblasts. The areas between the narrow columns of bone were filled with a young, loose connective tissue. Normal marrow remained in some areas.

The calcified mass of bone in the substance of the muscle was essentially similar to the skeletal bone. However, the columns of bone appeared thicker and the osteoclasts were fewer in number. There was fibrous replacement of the absorbed bone.

Sections of the cerebral cortex, basal ganglia, pons, medulla, cerebellum and cord were examined. No abnormality was noted. No other significant findings were noted upon examination of the gastrointestinal tract, adrenals, urinary bladder, ovary or breast.

### DISCUSSION

The pathologic findings in this case were of considerable interest. The parathyroid tumor was considered to be a carcinoma because it was found invading the esophagus, blood vessels and lymphatics, and had recurred after surgical removal. There have been 38 cases of carcinoma of the parathyroid gland reported up to 1946. The literature has been carefully reviewed by Norris<sup>12</sup> and will not be analyzed here. Norris accepted 12 of these 38 cases as carcinoma; three he considered questionable, while 23 he believed were wrongly diagnosed.

The other findings were those to be expected in a patient suffering from long standing hyperparathyroidism. The changes found in the kidney were similar to those described by Albright, Baird, Cope and Bloomberg<sup>8</sup> and Anderson.<sup>9</sup> The bone changes were those of osteitis fibrosa cystica generalisata (Albright). There was extensive metastatic calcification in the arteries, muscle, and uterus.

Acute parathyroid intoxication may be defined clinically as that stage of hyperparathyroidism wherein weakness, lethargy and intractable nausea and vomiting occur in association with an extreme elevation of the serum calcium level, often leading to death without apparent cause unless the hyperfunctioning tissue is removed.

Several theories have been advanced to explain the sudden death in this condition. Cantarow, Stewart and Housel<sup>7</sup> have described changes in various organs of dogs, particularly the heart and kidneys which they attribute to a direct toxic action of parathormone. This allegedly precedes the deposition of calcium and is somewhat similar to the toxic necrosis induced experimentally in vitamin D poisoning. These authors do not believe this effect is caused directly by the high serum calcium.

Shelling, Kajdi and Guth<sup>10</sup> have shown clearly in dogs that parathormone in repeated doses brings about a marked diuresis of water, chloride and fixed base with resultant dehydration, shock, azotemia and death. These authors were able to prevent a fatal outcome by the administration of large quantities of sodium chloride to replace the urinary loss.

Finally, it is possible that renal insufficiency resulting from fibrosis and calcification of the kidneys may be the cause of death in acute hyperparathyroidism as it is in the chronic form of the disease.

None of these theories can explain satisfactorily the cause of death in the present case. There was no pathological evidence of any unusual toxic necrosis. The heart itself revealed no more than the amount of intimal thickening of the coronaries which might be expected at this age. Medial calcification of the smaller arteries was present, but there was no necrosis or calcification of the myocardium. Although the renal insufficiency noted clinically and the kidney damage observed at autopsy undoubtedly played an important rôle in causing death, the degree of functional renal damage was not sufficient to account for death at the time and in the manner in which it occurred.

An excessive loss of serum base was unquestionably present during both episodes of acute parathyroid intoxication in this patient, as shown by the low level of serum chloride and carbon dioxide combining power and the excessive loss of chloride in the urine. Nevertheless, at the time of death there was no sign of progressive dehydration or increasing azotemia. Replacement of fluid and electrolytes failed to avert death, as it should have done according to Shelling's hypothesis.

We are left with no satisfactory explanation for the cause of death in this case. One possible finding of significance should be pointed out, however; that is, the rapid rise in serum calcium concentration during the last weeks of life. The effect of calcium in increasing the duration of cardiac systole and the opposite effect of potassium in inhibiting cardiac muscular irritability are well known. Hueper<sup>11</sup> in 1927 made the suggestion that in parathyroid poisoning cardiac systole might be prolonged to such an extent that congestive failure and circulatory collapse would result. It seems possible that the relatively sudden increase in the concentration of calcium perfusing the heart muscle in this patient may have increased cardiac muscular irritability to the point where ventricular fibrillation ensued. The calcium effect may well have been potentiated by the washing out of potassium incident to the administration of the large amounts of sodium salts which were given to combat the acidosis.

Whatever the cause of death, however, it is apparent in retrospect that this patient should have been operated on immediately under local anesthesia, without delaying in the futile attempt to correct a chemical imbalance the nature of which is not clear. The wisdom of this procedure is amply demonstrated by the dramatic improvement in this patient following operation in 1940 at a time when her serum calcium concentration had risen to 22.4 mg. per 100 c.c., a value comparable to that seen in fatal parathormone poisoning in dogs and reported by Hanes<sup>3</sup> in a fatal human case. In the present state of our knowledge the discovery and removal of a hyperfunctioning parathyroid tumor offers the only chance of survival in a similar circumstance.

This case, in respect to its pathology and recurrence, is quite similar to a patient now being followed by Lesses, Schlesinger, and Ober<sup>13</sup> at the Beth Israel Hospital. Their patient has had a locally invasive carcinoma of the parathyroid gland resected three times in two and one-half years. Each time the serum calcium returned to normal and then rose as the tumor recurred. Norris believes, and it is further emphasized by this case and the patient at the Beth Israel

Hospital, that, whenever possible, these tumors should be radically resected if recurrences are to be avoided.

### SUMMARY

A case of parathyroid carcinoma associated with long standing hyperparathyroidism and acute parathyroid intoxication is presented. The serum calcium level is one of the highest values reported in man. The theories of the mechanism of sudden death in parathyroid poisoning are discussed. It is suggested that the treatment of choice for parathyroid intoxication is prompt surgical intervention. It is emphasized that radical resection of parathyroid carcinomas should be employed where possible.

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## PULMONARY EDEMA IN THE COURSE OF TREATMENT OF MULTIPLE SCLEROSIS WITH PROSTIGMINE: A REPORT OF TWO CASES \*

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WIDESPREAD use of prostigmine has shown it to be a useful drug. Like all other powerful medications, its administration is associated with occasional untoward side reactions. In the following, we are reporting our observations on two cases of multiple sclerosis in which pulmonary edema occurred in the course of treatment with prostigmine. Careful review of the literature reveals only one case<sup>5</sup> of multiple sclerosis complicated by pulmonary edema and no instances of pulmonary edema attendant upon prostigmine therapy. It is perhaps appropriate to mention that we have seen several patients in the past with multiple sclerosis who, while under treatment with prostigmine, developed respiratory embarrassment and moist râles in both lungs. At that time, we were unable to classify the conditions. In the two cases reported below, however, pulmonary edema was manifest.

### CASE REPORTS

*Case 1.* E. D., a 40 year old, white male speech teacher, was admitted February 17, 1947, with chief complaints of inability to walk, difficulty in speaking, defective vision and tremors on purposive movement of the upper extremities. His illness began in 1932 when he had areas of transitory numbness under his nose and on his left temple. The next year, he developed diplopia which lasted two months, and in 1936, his left foot began to drag and slap the ground. Progressive weakness and tremors intensified by voluntary movement gradually involved his neck and all four extremities. For four years before admission vision had been deteriorating; for three years he had had occasional urinary incontinence.

He had no complaints referable to his cardiovascular system nor any history of rheumatic fever. Past history and family history were non-contributory.

Neurological examination revealed the following: Marked head tremor, scanning speech, vertical and horizontal nystagmus and temporal pallor of the optic discs; pupils reacted well to light and in accommodation; there was marked ataxia in the upper extremities; considerable spasticity was present in the lower extremities; deep tendon jerks were hyperactive, abdominal reflexes were absent; there were bilateral Hoffmann and Babinski signs and ankle cloni. Diminished vibratory sensation over the left iliac crest constituted the only sensory disturbance. Spinal tap revealed an initial pressure of 180 mm., final pressure of 110 mm. after removal of 10 c.c. of fluid, 62 mg. of protein, and a colloidal gold curve of 01110000. Diagnosis was made of multiple sclerosis.

Systemically, there were no pathological findings. The heart sounds were normal, and no murmurs were heard. Lungs were clear on auscultation and percussion. Chest roentgen-ray showed the heart to be normal in size, contour and position. Electrocardiogram was normal. Blood pressure on admission was 130/86. Decholin time was 10 seconds. Pulse rate remained between 80 and 90. Urine and blood morphologies and chemistries were normal.

Therapy consisting of prostigmine, 15 mg. t.i.d. by mouth was begun February 22, 1947 and given daily until February 26. In the evening of this date, he received

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From the Department of Neurology, Goldwater Memorial Hospital.

a soapsuds enema of about two quarts. A minute or two after that, he became acutely ill, developing the picture of acute pulmonary edema. He gasped for air, became clammy and cyanotic, and white foam poured from his mouth and nose. Showers of moist râles were heard over both lungs. Blood pressure was 140/80; pulse was 60. He was given morphine sulfate, gr. 1/6 by hypodermic, oxygen, and tourniquets were wrapped around his extremities. He responded slowly, and about six hours later, his chest was practically clear. The patient was conscious throughout the attack and complained of no pain. Blood pressure from his admission until the present time has not changed. His electrocardiogram also has not changed.

Prostigmine therapy was discontinued. Two weeks later, a two-quart soapsuds enema gave no symptoms.

On July 13, 1947, he was again given oral prostigmine, 15 mg. twice a day, by another staff member. On November 29, 1947, he developed another attack of typical pulmonary edema, in every respect similar to, but somewhat milder than the original.

*Case 2.* T. L., a 47 year 'old white woman, was admitted July 13, 1939, with chief complaints of loss of vision in her right eye for three years and inability to walk and to use her fingers and hands for two years.

Neurological examination revealed the following findings: Complete optic atrophy in the right eye and temporal pallor of the left disc; normal, reactive pupils; weakness of the entire left side; hyperactive reflexes in the left lower extremity, sluggish reflexes in the right upper extremity, absent abdominal reflexes; bilateral Babinski and confirmatory signs and bilateral Hoffmann signs; ataxia of the right lower extremity; no sensory changes. A diagnosis of multiple sclerosis was made. The patient's condition progressed until 1945, at which time she had spastic paraplegia, hyperactive reflexes throughout and a loss of vibration and position sensations in upper and lower extremities. Spinal tap in 1940 was within normal limits.

There were no complaints of cardiovascular symptoms; no history of rheumatic heart disease. Past and family histories were not significant.

General physical examination revealed no pathologic abnormalities. There were no heart murmurs, and lungs were clear on percussion and auscultation. Chest roentgenogram and electrocardiogram were normal. Blood pressure was 134/86. Pulse ranged between 80 and 90. Barium enema showed a megacolon. Blood and urine examinations were normal.

From December, 1946, she received prostigmine orally 15 milligrams t.i.d. until January 5, when it was increased to 30 milligrams four times a day. This was levelled off at 25 milligrams four times a day on January 20, and she was maintained on this dosage until March 1. In the morning of March 1, while receiving an oil retention enema, she became restless, perspired profusely, developed tracheal rattling which could be heard at a distance and foamed at the mouth. Numerous râles were heard over both lungs. Heart rate was 60. She responded to the same treatment mentioned previously, viz., morphine sulfate, oxygen and tourniquets. Neither blood pressure nor electrocardiogram was changed after the attack.

#### COMMENT

The majority of all cases of pulmonary edema occur in cardiovascular disease; left ventricular failure is usually considered to be the chief direct cause. Pulmonary edema, however, may be found in a variety of other conditions in which the heart is free from disease, and in which the mechanism of its development is evidently different.

According to current textbooks, pulmonary edema may occur as a result of mechanical disturbances in the pulmonary circulation (embolism, tumor, etc.),

inflammation of the lungs (pneumonia), disturbances in the vasomotor apparatus, chemical irritation (contact with poisonous gases); or finally, injection of substances like chloral hydrate, muscarin, adrenalin, morphine, etc. There are also case reports<sup>1</sup> of pulmonary edema in drowning, after paracentesis of thoracic or abdominal cavities, in shock (electric, anaphylactic, insulin), beri-beri, thyroid crisis, nephritis, uremia, etc. Recently, a case was reported<sup>2</sup> in which laceration of the lung was followed by pulmonary edema. There is, furthermore, a considerable number of observations to the effect that this condition may occur in the course of diseases of the central nervous system.<sup>3, 4</sup> It has been reported in cases of trauma to the skull, brain injury, brain tumor, cerebral hemorrhage, meningitis, encephalitis, tabes, poliomyelitis, etc.

To our knowledge, multiple sclerosis complicated by pulmonary edema has been reported only once.<sup>5</sup> The patient in question had dyspnea, râles over both lungs, tracheal rattling and a temperature ranging between 100° and 104° F. for several days. At necropsy, patches of bronchopneumonia were found. The diagnosis of pulmonary edema in this case is not beyond doubt.

More is known concerning the relationship between administration of prostigmine or physostigmine and subsequent pulmonary edema, although these drugs have been given in innumerable cases without any ill effects. In laboratory animals, pulmonary edema is a usual finding in poisoning by cholinergic drugs in general.<sup>6</sup> Action of prostigmine or physostigmine has been divided into nicotinic and muscarinic components.<sup>7</sup> The more prominent effects of stimulation of respiratory glands and the constrictor effect on the muscles of the bronchi are collectively comprised in muscarinic action. Muscarine itself produces pulmonary edema, which in experiments<sup>8</sup> was found to be characterized by fall in blood pressure, bronchoconstriction and overfilling of pulmonary vessels; atropine and adrenalin relieved the bronchospasm and spared the animal's life. True, hyperacute secretion of respiratory glands may by itself produce the clinical picture of edema of the lungs; microscopic evidence indicates, however, that cholinergic drugs lead to true pulmonary edema with transudation into the alveoli.<sup>6</sup>

The constriction of bronchial muscles is regarded as a potent factor in the development of edema.<sup>9</sup> The assumption is that bronchial constriction and increased secretion of respiratory glands impede free inflow of air. Consequent anoxia renders the dilated pulmonary vessels more permeable, and then the suction of the descending diaphragm on the incompletely closed mechanical system draws fluid from the vessels into the alveoli. It was claimed<sup>10</sup> that the bradycardia caused by prostigmine or physostigmine induces dilatation and consequently increased permeability of the pulmonary vessels.

Additional light is thrown upon the connection between the autonomic nervous system and pulmonary edema by the experience gained from experiments and operations on the autonomic nervous system in the neck. Bilateral vagotomy in the neck is known to be followed by pulmonary edema after one or two days. It develops almost immediately if the operation is accompanied by an intravenous infusion of saline.<sup>11</sup> In a case<sup>12</sup> of cancer of the esophagus, both vagi were crushed during bouginage of the stricture. Fatal pulmonary edema developed within half an hour. On the other hand, injection of the vagus with procain<sup>13</sup> has been used with success to relieve pulmonary edema in cardiac patients. It may appear paradoxical that cutting the vagi gives opposite effects from blocking them with procain; however, one has to consider that these procedures may

give different results, because cutting may involve an initial stimulus. Another difference may lie in the selective affinity of procain for nerve fibers of different quality. The theory<sup>14, 15</sup> was advanced that the vagi control the permeability of the lung structures and vessels.

Two cases of fatal poisoning with physostigmine have been culled from the literature of the past 16 years, to wit:

1. The day after herniorrhaphy, a patient received an injection, by mistake, of 100 mg. physostigmine (for veterinary use) in an attempt to stimulate bowel movement. He died of pulmonary edema within 30 minutes.<sup>16</sup>
2. A 19 year old girl complained of pains in her kidney region which were diagnosed as of sympathicotonic origin. A subsequent injection of physostigmine 1.2 mg. was followed by death in 15 minutes from pulmonary edema. At autopsy, all organs were found to be normal except the lungs; they were filled with serosanguineous fluid.<sup>17</sup>

It is notable that the dose of physostigmine used in the latter case is well within the limits of the therapeutic range. Non-fatal cases may not have been brought to public attention. Dr. J. Wilder, in an unpublished communication, mentions that he saw a case of myasthenia gravis which developed pulmonary edema while under intensive treatment with prostigmine.

In both our cases presented here, attacks of pulmonary edema followed immediately upon the administration of enemas. Since the lower and middle hemorrhoidal veins empty into the inferior vena cava, two quarts of fluid in the one case certainly may have tended to flood the lungs when absorbed rapidly. Much more controversial is the relationship of the oil retention enema in case 2 to the development of pulmonary edema. However, there are reports<sup>4</sup> that rapid distention of hollow viscera may be a factor in causing pulmonary edema, perhaps representing thus a kind of additional parasympathetic stimulus. An effect of such distention on the coronary circulation has been described.<sup>18</sup>

Prostigmine has an effect on voluntary muscle<sup>7</sup> apart from its nicotinic and muscarinic actions. It is this action on the neuromuscular junction which determines its therapeutic use in neurological conditions, e.g., myasthenia gravis, parkinsonism, multiple sclerosis, etc. This particular therapeutic effect of prostigmine on muscles is blocked by curare and by quinine, but not by atropine. It is therefore suggested that prostigmine be combined with atropine to avoid any untoward effects of the muscarinic action of prostigmine.

#### SUMMARY

Two cases of multiple sclerosis are reported in which attacks of pulmonary edema with recovery were observed during treatment with prostigmine immediately following enemas. The various factors which may have contributed to the development of pulmonary edema in these cases have been discussed, and the relative importance of the treatment with prostigmine noted. It is suggested that prostigmine be combined with atropine to avoid untoward side effects.

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### LIPOID GRANULOMATOSIS (XANTHOMATOSIS) WITH MARKED PULMONARY FIBROSIS AND COR PUL- MONALE AS OUTSTANDING MANIFESTATIONS \*

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LARGELY as a result of the contributions of Hand,<sup>1</sup> Schüller,<sup>2</sup> and Christian,<sup>3</sup> "xanthomatosis" of the skeletal type became clearly established as a disease found principally in children. The clinical manifestations of the peculiar pathological process were described as defects in membranous bones, exophthalmos and diabetes insipidus, and were all attributable to "xanthomatous" involvement of membranous bones (chiefly skull) and of the hypothalamus. Since these early case

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From Lebanon Hospital and The Bureau of Tuberculosis, Dept. of Health, New York City.



reports, the same pathological process has been found in other patients, not a few of them adults. It seems obvious now that the earlier cases with skull defects, exophthalmos and diabetes insipidus represented merely the first recognized instances of a peculiar lipid granulomatosis (or xanthomatosis),<sup>4, 5</sup> and that the symptomatology of the disease depends entirely on the location, number, and size of the lesions. Thus, many bones other than the skull, including long bones, have not infrequently been involved and, likewise, the skin, lymph glands, and many other organs have been implicated in various cases.

The diagnosis of lipid granulomatosis in the absence of the Hand, Schüller-Christian triad (defects of membranous bones, exophthalmos and diabetes insipidus) has not received much attention. Only a few cases so diagnosed have been reported.<sup>4</sup>

Regardless of the causative factor or factors of the disease, concerning which there is difference of opinion, certainly the reticulo-endothelial system is outstandingly involved. Wherever there is reticulo-endothelial tissue there may conceivably be found the characteristic pathological lesion of the disease. There is unanimity of opinion in respect to involvement of the reticulo-endothelial system among workers who otherwise have different views as to the pathological physiology.

Pulmonary infiltration has been observed by a number of authors.<sup>6, 7, 8, 9, 10</sup> Most often it proves to be an incidental finding discovered in the course of chest roentgen-ray, in a patient with other symptomatic manifestations of the disease. Pulmonary infiltration extensive enough to result in congestive right heart failure (as in the following case) is distinctly rare. We have encountered no case in the literature in which symptoms in an adult patient were exclusively referable to pulmonary involvement and resultant right heart failure. There are pathologists of wide experience who have not seen this pulmonary cardiac combination in their postmortem material of lipid granulomatosis (xanthomatosis).<sup>11</sup> Of interest in our case also is the fact that in a preemployment chest roentgenogram at least two years before symptoms of the disease appeared, there was evidence of extensive pulmonary infiltration.

#### CASE REPORT

The patient, a married white male, an American of Scotch-Irish ancestry, age 35, consulted one of us on July 8, 1946, because of general weakness and progressively increasing shortness of breath on effort. In August, 1940, he had been examined by us for a slight cough and hoarseness of six days' duration. Further inquiry at that time revealed that there was recent slight dyspnea on effort, but this in no wise interfered with the patient's ordinary social or occupational activities. In March, 1938, prior to employment by the New York City Health Department, a routine chest roentgen-ray was taken, the subject being completely free of symptoms. The film (figure 1) disclosed uniformly fuzzy, bilateral symmetrical infiltrations throughout both lung fields, as well as hilar thickening.

Physical examination on August 11, 1940, had revealed a well-nourished, healthy-looking young male adult, age 29 years, whose only positive findings were scattered medium-sized rhonchi at both lung bases. A roentgenogram of the chest revealed a mottling throughout both lung fields which differed little from that in the chest film of March, 1938. Cardiac configuration and size were normal. Sputum examinations were repeatedly negative for tubercle bacilli, and blood Wassermann test, blood count, sedimentation rate and urine examination revealed no abnormalities. The diagnosis

of pneumoconiosis could not be entertained inasmuch as no history of employment in a dusty trade was elicited. Likewise, studies with respect to possible fungus etiology were negative. The clinical impression at that time was that of diffuse pulmonary fibrosis, but admittedly no etiological factor was ascertainable.

Cough and hoarseness cleared up entirely approximately one week after onset, and in all likelihood resulted from an intercurrent respiratory tract infection. The patient was studied again in June, 1941, at which time the slight dyspnea on moderate effort, physical and roentgen-ray findings, were precisely as in August, 1940.

Owing to our absence from civilian practice during the war years, the patient was not seen again until July 8, 1946. His general condition had progressively



FIG. 1. Preemployment chest roentgen-ray. Patient asymptomatic. Extensive pulmonary infiltration and hilar thickening. Heart not enlarged.

deteriorated since 1941. There was now marked, general asthenia, loss of weight from 141.5 lbs. (in August, 1940) to 126 lbs., and marked dyspnea after slight physical effort. This symptom had made it necessary for the patient to quit his occupation as a foreman in an electrical wire factory.

Family history revealed no pertinent data. Past history disclosed only that the patient had had measles in childhood. Reference has already been made to the pre-employment roentgen-ray film taken of this patient's chest in March, 1938.

Physical examination now revealed a malnourished, chronically ill male, appearing older than his actual age of 35. There was slight cyanosis of the lips and cheeks

Dyspnea was marked even at rest, and accentuated by recumbency. Pulse was regular and 112 per minute. There was no exophthalmos. Palpation of the scalp revealed, in the right parietal region, a slightly tender, irregular area of depression of the osseous vault, approximately constituting a quadrilateral area, 8 cm. by 5 cm. At this juncture in the examination the patient volunteered the information that this area of the scalp had been slightly tender for approximately a year. There was no cervical or other adenopathy, nor was there thyroid enlargement. Neck veins were definitely engorged. Chest examination revealed slight dullness over the entire lung area,

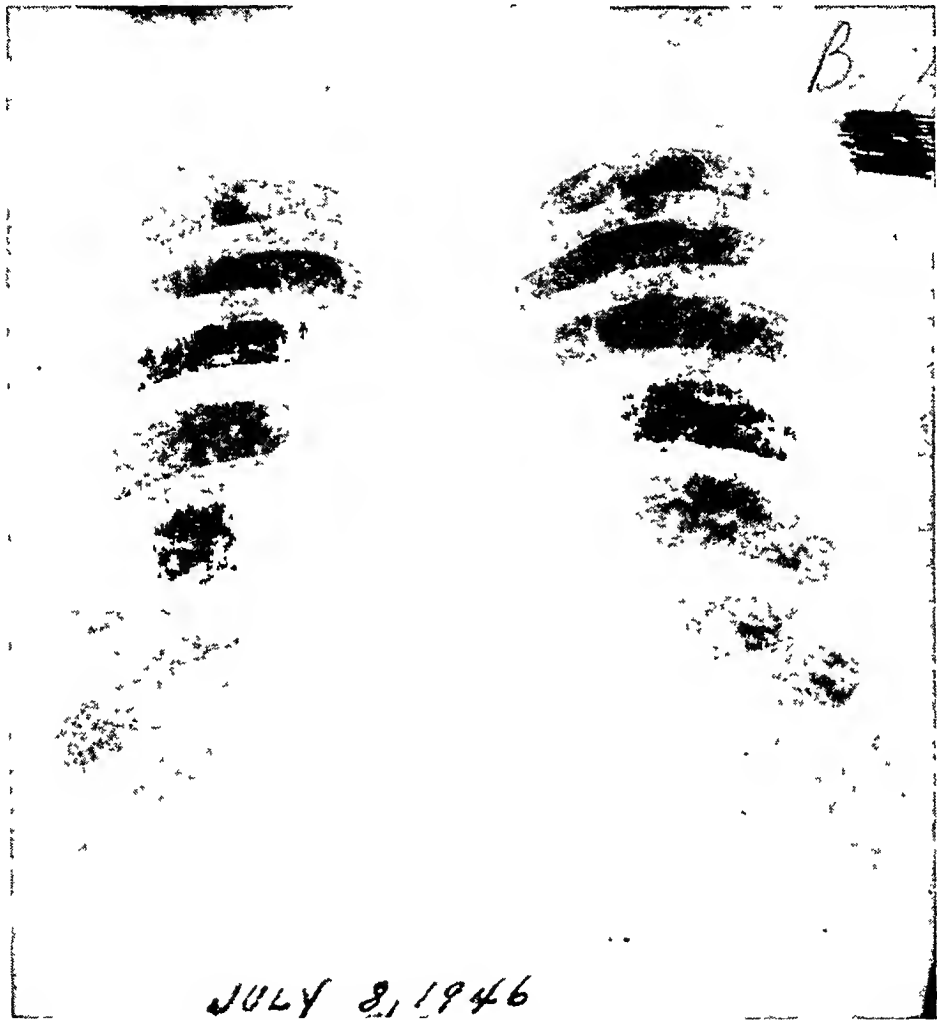


FIG. 2. Illustrates extensive pulmonary fibrosis and definite cardiac enlargement.

somewhat more marked over both lower lobes. Small-sized rhonchi were audible on inspiration and expiration over the entire lung area, but over both lower lobes the rhonchi were louder and more sustained. The heart was enlarged both to the right and left, the maximum apex impulse being palpable 1.5 cm. outside the midclavicular line in the fifth intercostal space. There was sinus tachycardia of 112 per minute and all heart sounds were of poor quality. Abdominal examination revealed the liver to be uniformly enlarged, firm, and slightly tender, its lower edge palpable at the level of the umbilicus. There was slight bilateral, pretibial edema.

Radiographic examination of the chest (figure 2) revealed an extensive interstitial fibrosis throughout both lungs from apex to base. The heart was moderately enlarged, with definite prominence of the pulmonic conus and enlargement of the left ventricle and right ventricle. A roentgenogram of the skull (figure 3) disclosed a large, irregular, "geographic," quadrilateral area of bone destruction in the right parietal region, approximately 8 by 4 cm. in extent.

With these findings it seemed quite clear that the patient was suffering from an advanced degree of diffuse pulmonary fibrosis with resulting chronic cor pulmonale. The presence of an extensive osseous lesion in the skull made it seem likely that the



FIG. 3. Extensive geographic skull defect, right parietal region.

pulmonary findings were not merely those of an isolated pulmonary disease, but rather an incident in the course of a widespread pathological process affecting at least bone and lung. The general appearance of the skull lesion suggested the possibility of lipoid granulomatosis.

Further laboratory and radiographic data were as follows: Urine, faint trace of albumin; repeatedly negative for Bence-Jones protein. Blood Wassermann test negative; hemoglobin 17.05 grams, red blood cells 5,190,000; neutrophils 69 per cent; lymphocytes 28 per cent; mononuclears 1 per cent; bands 2 per cent; blood sugar 93 mg. per cent; non-protein nitrogen 32 mg. per cent; serum albumin 5 per cent; serum

globulin 2.2 per cent; phosphorus 7.4 mg. per cent; total cholesterol 237 mg. per cent; cholesterol esters 91 mg. per cent; alkaline phosphatase 3.3 KA units; acid phosphatase 0.8 KA units; calcium 8.6 mg. per cent; lecithin 140 mg. per cent.

Radiographic examination of the upper two-thirds of right femur disclosed several small cystic areas of bone destruction in the shaft with thickening of the cortex along the upper third. Roentgen-ray study of the left hip and upper two-thirds of the left femur disclosed cystic areas of bone destruction in the descending ramus of the left pubic bone. There was thickening of the cortex of the middle third of the shaft

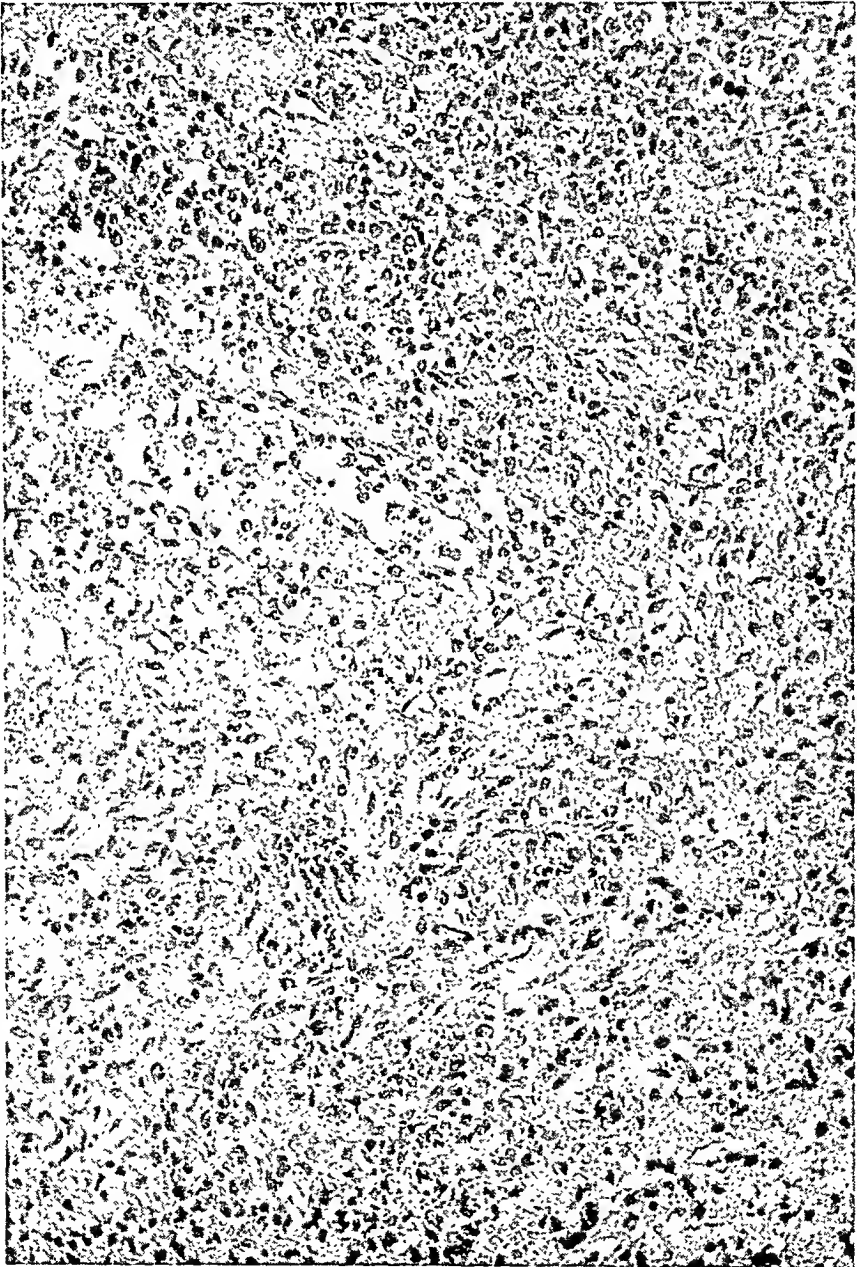


FIG. 4. Microscopic section illustrating histiocytes, foam cells, and other characteristics described in text.



FIG 5 Illustrates dural attachment to lesion

of the left femur along the medial aspect. A few lineal areas of bone destruction were noted in the cortex. Other skeletal roentgen-rays were negative. An electrocardiogram disclosed evidences of right ventricular strain.

On August 29, 1946, a biopsy of the lesion of the right parietal bone was performed at Lebanon Hospital, New York City. This was reported as follows by Dr. Joseph C. Ehrlich and Dr. H. Cohen (figure 4). *Gross Specimen:* Received four small pieces of tissue. One measures 7 by 4 by 2 mm. and has a solid consistency. One-half of it is uniformly brown-gray in color and the other half is dark yellow with little light yellow nodules within it. Two other specimens are small fragments, solid,

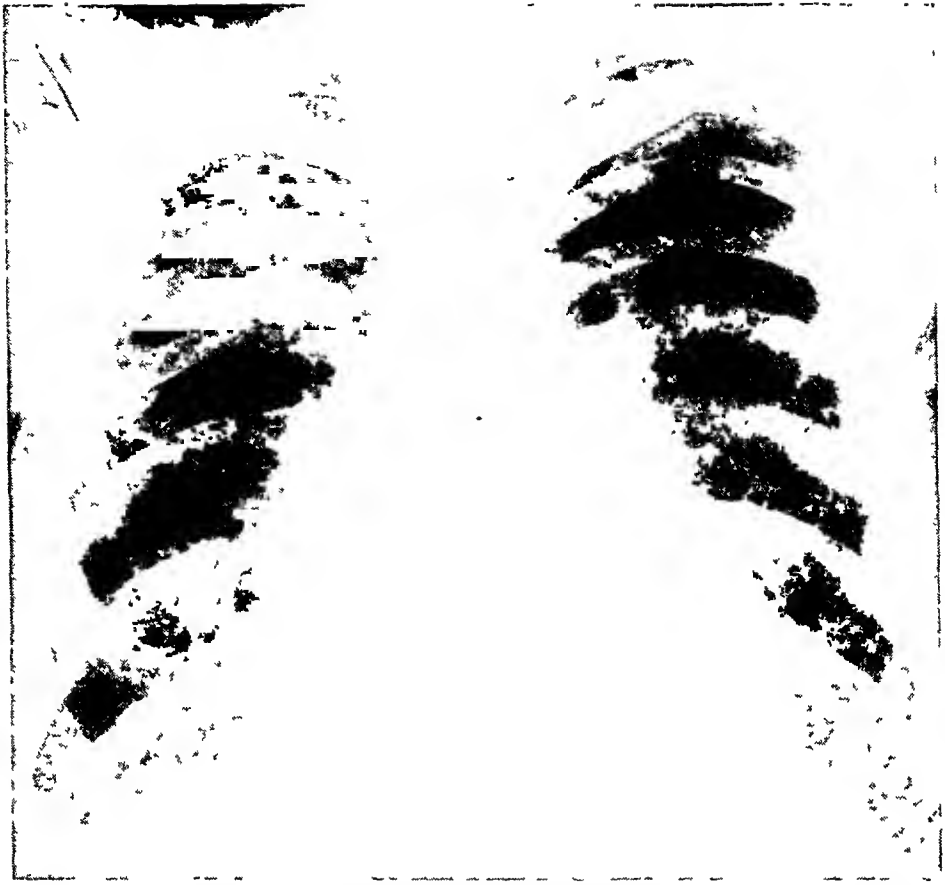


FIG. 6. Pulmonary infiltrations less marked after roentgen therapy Cardiac enlargement increasing.

and yellowish in appearance. One is somewhat firm and seems to have a layer of dura on it. The fourth piece is a small piece of tissue with a calcified spicule at one edge. Received also another small piece of tissue 6 mm. long taken from the same area for frozen section.

*Histopathologic Findings.* The fragments of tissue are composed of the following elements: (1) sheets of medium-sized stellate histiocytic cells with finely granular cytoplasm in which, occasionally, finely granular pale brown pigment is present. These cells are sometimes multinucleated; (2) numerous eosinophilic leukocytes, lymphocytes, and moderate numbers of neutrophilic leukocytes and plasma cells; (3) moderate numbers of thin-walled congested blood vessels; occasional large fresh extravasations of erythrocytes; (4) relatively acellular dense fibrous tissue; and (5) a tiny fragment of bone whose trabecular architecture appears essentially normal.

The fragment of tissue available for frozen section consists essentially of fibrous connective tissue and inflammatory cellular elements but relatively few histiocytes. It is probably derived from the dura. Sections of this fragment were examined in polarized light and also after staining by Sudan IV. Numerous tiny doubly refractive crystals and moderate amounts of tiny Sudanophilic droplets were found. Both the doubly refractive crystals and the Sudanophilic droplets were dispersed throughout this tissue along collagen fibers and in vascular septa.

One small zone of necrosis is present. A number of large foam cells in this area may be of simple reactive origin.

The general histopathologic pattern of this granuloma is consistent with the diagnosis of Schüller-Christian disease.

*Diagnosis.* Lipoid granuloma of skull (of the type seen in Schüller-Christian disease).

In spite of low salt diet, fluid limitation, and digitalis administration, all the symptoms in this patient have progressed strikingly. Beginning October 3, 1946, the patient was given deep roentgen-ray treatment to the anterior and posterior chest fields, at five-day intervals, a total of 800 r, 200 K. V. through  $\frac{1}{2}$  cu. and 2 al. filter.

On December 27, 1946, because of increasing enlargement of the liver, with abdominal fullness and markedly increased pretibial edema, intravenous mercurial therapy was instituted twice weekly, in 2 c.c. doses. This has failed to control the increasing peripheral edema and hepatic enlargement. On January 21, 1947 (figure 6), a chest roentgen-ray film disclosed increased cardiac enlargement. The pulmonary infiltration, while still pronounced, appeared less marked than that of July 8, 1946, probably the result of roentgen therapy. In spite of the treatment already detailed, examination of February 25, 1947, reveals marked orthopnea and increased size of the liver, as well as increased peripheral edema.

### COMMENT

The finding of notable pulmonary fibrosis in a pre-employment chest roentgen-ray, when this patient was otherwise well, is, we believe, of clinical interest. During the course of chest roentgen-ray surveys conducted among presumably well persons, with the intent of detecting early tuberculosis, the presence of so-called pulmonary fibrosis is not infrequently discovered. Confronted with such an instance, the clinician embarks on a search for etiological factors. Usually the possibility of lipoid granulomatosis is not considered. It now seems to us that in any instance of otherwise unexplained pulmonary fibrosis, especially in children or young adults, this entity must be kept in mind. Further interrogation of the patient and bone roentgen-rays, especially of the skull, may conceivably add other cases similar to ours. Perhaps if complete investigation fails to reveal an etiological factor for pulmonary fibrosis, lung puncture is justified for biopsy. Possibly in our case such a diagnostic measure might have led to an earlier diagnosis than was made. So far as we know, lung puncture has not been given serious consideration in the diagnosis of lipoid granulomatosis.

Early diagnosis is not merely an academic consideration. While reports of treatment by irradiation of osseous lesions in this disease have been commented on favorably by various authors, accounts of treatment of pulmonary lesions by x-ray are rare. Currens and Popp<sup>12</sup> reported a definitely favorable therapeutic response in their case. Immler<sup>13</sup> states that roentgen therapy in moderate doses causes a definite therapeutic response. Early treatment when the pulmonary infiltration is predominantly granulomatous may be expected to be of greater effectiveness than that administered when fibrous tissue predominates, a change which is part of the evolution of this disease and one that is likely to render irradiation fruitless.

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## SIMULTANEOUS ASSOCIATION OF SITUS INVERSUS, CORONARY HEART DISEASE AND HIATUS HERNIA: REPORT OF A CASE AND REVIEW OF LITERATURE \*

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CONGENITAL dextrocardia with situs inversus is an infrequent but not a rare condition, estimates as to its incidence varying from one in approximately 35,000 individuals<sup>1</sup> to one in 6 to 10,000.<sup>2, 3, 4, 5</sup> The association of congenital dextrocardia with coronary heart disease is, however, quite rare,<sup>6, 7</sup> only five such case reports appearing in the literature. No case of hiatus hernia occurring with situs inversus has yet been reported. For this reason it was felt that the report of the following case presenting the coexistence of situs inversus, coronary heart disease and hiatus hernia would be of interest.

### CASE REPORT

The patient, a 54 year old Armenian-born, retired storekeeper, consulted one of us (H. R.) with a chief complaint of recurrent pain in the chest of approximately five years' duration. He had enjoyed good health until five years ago, when following a mild illness of one week's duration marked by cough, he noticed the onset of episodes of pain in the upper anterior chest just to the right of the sternum. At that time he was seen at a community hospital where, after roentgen-ray examination, he was told "there was something wrong in his chest." Two years before, because of progression of his symptoms, he was seen at a large clinic, where he was informed that he had

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heart disease. Nitroglycerine was prescribed, which effectively and rapidly relieved the pain. During the past two years, however, the attacks had increased in frequency and severity, necessitating his retirement from business and reducing him to a semi-invalid status. Mild exertion or emotion of moderate intensity precipitated the episodes of pain, which was described as a sensation of pressure or constriction in the upper chest to the right of the sternum. The pain radiated to the shoulders and down both upper extremities, apparently equally, and was associated with numbness

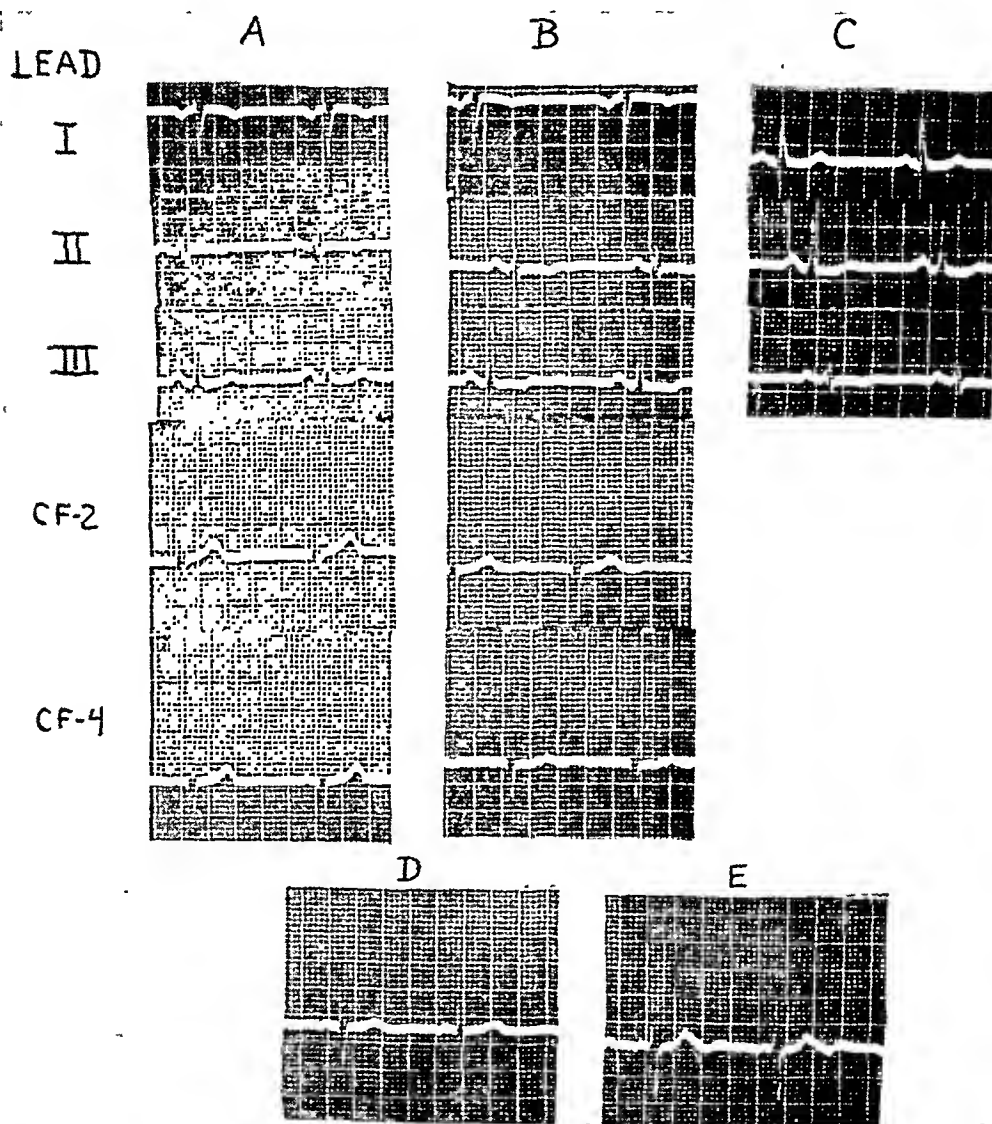


FIG. 1. Column A represents EKG tracings at rest. In Column B are the tracings obtained during the recovery phase (10 minutes) following 20 trips on the 2 step staircase; the amplitude of the T-waves in each lead is diminished, as compared with A, and T<sub>s</sub> (equivalent to T<sub>2</sub> in sinistocardia) has become diphasic. Column C shows the resting electrocardiographic limb leads "corrected for dextrocardia" by reversal of the arm electrodes. D is the tracing (CF<sub>4</sub>, obtained with the patient standing) immediately prior to the exercise tolerance test; E is the corresponding tracing immediately following completion of the test, at the time of anginal pain. The increased amplitude of T is striking.

In all fourth lead tracings the correction for dextrocardia has been made, the chest electrode being placed on the right chest, its position and nomenclature corresponding to those employed when the precordium is on the left.<sup>42</sup>

in the forearms and hands. In addition to exercise, which constantly induced an attack of pain, the ingestion of a heavy meal was often followed by chest pain subjectively indistinguishable from that associated with exertion and also relieved by nitroglycerine. Attacks were frequently nocturnal, waking him from sleep; he had discovered empirically that abstaining from all food after 5 or 6 p.m. and sleeping in a semi-recumbent position were measures which diminished the frequency of these nocturnal episodes. There had been no abdominal pain, dysphagia, nausea, vomiting, or excessive belching; no dyspnea, orthopnea, chronic cough or swelling of the ankles. At the time of examination he was taking 8 to 10 tablets of nitroglycerine daily.

The past history was non-contributory. The family history revealed that a brother had died of myocardial infarction at the age of 42; there was no history of congenital abnormalities in other members of the family, or of consanguineous marriage.

Physical examination: Temperature 98.0° F., pulse rate 70 per minute, respiratory rate 20. The head and neck were normal; the fundi revealed no evidence of arteriosclerosis. The chest was somewhat emphysematous. The cardiac apex impulse was palpable in the fifth right interspace in the mid-clavicular line; there was no evidence of cardiac enlargement to percussion. A grade 2 apical, non-transmitted systolic murmur was audible. The blood pressure was 130 mm. of mercury systolic and 84 mm. diastolic. The abdomen revealed no masses, tenderness or spasm; hepatic dullness extended down to the left costal margin. The right testicle was lower than the left. The extremities were normal. Neurological examination revealed no abnormalities. The patient had always been right handed.

Laboratory studies: Hemoglobin (Sahli) was 94 per cent, the red blood cell count 4.9 million per cubic millimeter, the white blood cell count 7,500 with a normal differential. The Hinton test was negative. Urine examination was negative. Guaiac tests on the stool on several occasions revealed no occult blood. Roentgen-ray of the chest confirmed the clinical impression of dextrocardia. The heart was of normal size and shape; the aortic knob was somewhat prominent. The lung fields were normal, and there was no evidence of bronchiectasis. Electrocardiogram (figure 1) revealed the changes typical of congenital mirror-image dextrocardia; all complexes of Lead I were inverted, and Leads II and III were transposed as compared with records of individuals in whom the organs are more conventionally disposed. (For comparison, the electrocardiographic records obtained from the patient by reversing the arm electrodes are also shown in figure 1 C.) The low voltage of the T-waves in all leads and the diphasic T<sub>2</sub> (corresponding to the conventional T<sub>2</sub>) are suggestive of myocardial disease.

A gastrointestinal series revealed a small hiatus hernia (figure 2), a portion of the cardiac part of the stomach being visible above the diaphragm adjacent to the esophagus. The shadow of the liver was visualized in the left upper quadrant, that of the spleen in the right upper quadrant of the abdomen.

Aminophylline, 3 grains orally four times a day was prescribed, but it did not effect appreciable change in the symptomatology, nor diminish the need for nitroglycerine. However, when syntropan, 100 mg. thrice daily was given, some diminution in the severity of the attacks ensued. The further addition of 20 drops of tincture of belladonna q.i.d. to the therapeutic regimen practically eliminated the nocturnal attacks and reduced the diurnal episodes to three or four per day.

## DISCUSSION

It has been stressed repeatedly in recent years that hiatus hernia may be responsible for episodes of chest pain very closely simulating angina pectoris associated with coronary heart disease.<sup>8, 9, 10, 11, 12, 13, 14, 15</sup> In an attempt to

evaluate more clearly and objectively what part of the symptomatology in this case was of cardiac origin, it was deemed advisable to test coronary sufficiency. A safe and reliable <sup>16</sup> estimate of the adequacy of the coronary circulation is obtained by the exercise tolerance test, in which the subject performs a certain amount of work, and observation is made of both the onset of anginal pain and change in the electrocardiographic pattern immediately before and after exercise.<sup>17</sup> It was found on several tests on different occasions in the patient under discussion that after approximately 20 trips on the two-step staircase, chest pain identical with that characterizing the patient's illness occurred; and the electrocardiogram

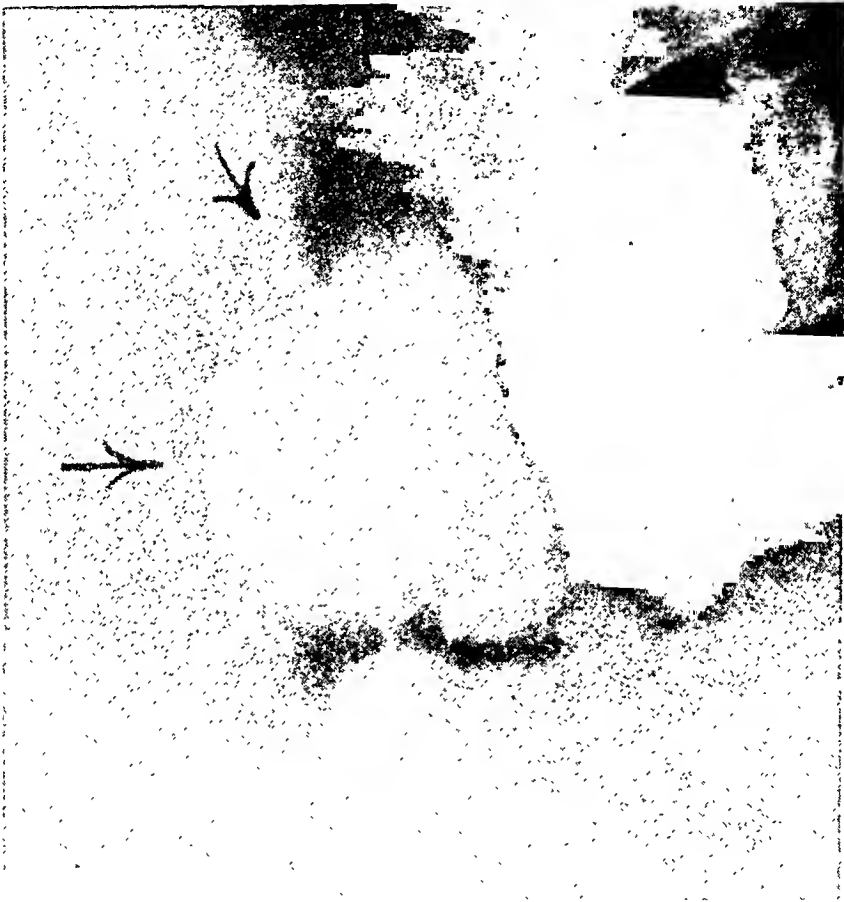


FIG. 2. Appearance of hernia following ingestion of barium meal (arrows).

immediately following the exercise showed significant changes from the pattern prior to exertion; figure 1E illustrates the rise in amplitude of  $T_4$  occasioned by exercise. Riseman and his colleagues <sup>17</sup> have pointed out that Lead IV more regularly than the limb leads shows these changes during and after angina; they observed that although both normal individuals and those with angina pectoris may show T-wave depression following exercise, increased amplitude of  $T_4$  was noted only in the latter. It has been observed that in the chest pain associated with hiatus hernia, unlike that of angina pectoris due to coronary heart disease, there is no constant relationship between exertion and the induction of pain.<sup>8, 12</sup> In our patient such a constant relationship did exist, both from the clinical history

and from the observation of the exercise tolerance tests, in which pain always followed the performance of approximately the same amount of work.

In summary, from the character of the pain and its radiation, from the constancy of the relation between exertion and pain, from the response to nitroglycerine, from the electrocardiographic suggestion of myocardial disease, and from the characteristic electrocardiographic changes in the exercise tolerance test, the diagnosis of coronary heart disease with angina pectoris seems firmly established. The contribution of the hiatus hernia to the symptomatology is difficult to evaluate precisely, but the following considerations indicate that a component of the pain was due to this condition: (a) chest pain occurring at rest was invariably nocturnal, occurred in recumbency, and could be largely prevented by the eating of small meals and by assuming an upright posture; the relationship of the pain due to the hiatus hernia to the ingestion of food and the influence of position upon it are well known<sup>12, 13</sup>; (b) the administration of syntropan and belladonna, agents which are ineffective in the treatment of the pain of coronary heart disease<sup>18</sup> but often effective in hiatus hernia, caused reduction in the severity and frequency of the nocturnal attacks but was without influence on the attacks of pain precipitated by exercise, which were promptly relieved by nitroglycerine. It seems clear that this patient therefore presents congenital dextrocardia with situs inversus on roentgenological evidence, coronary heart disease with angina pectoris on the basis of the clinical and electrocardiographic findings, and symptomatic hiatus hernia, demonstrated by roentgen-ray, the clinical history and the favorable response to antispasmodics and diet.

#### COMMENT

The rarity of acquired organic heart disease in individuals presenting dextrocardia with situs inversus has been noted by several observers<sup>6, 7, 19, 20</sup>; the infrequency of the association is even more striking when it is seen that situs inversus itself is apparently more common than is generally realized, the incidence in the general population being approximately one in ten thousand. In table 1 we have compiled from the literature some of the figures on the frequency of congenital dextrocardia. The rarity of the association of acquired heart disease with situs inversus is in marked contrast with the positive correlations existing between situs inversus and congenital abnormalities (in addition to the dextrocardia) of the cardiovascular and other systems<sup>21, 22</sup> and especially between bronchiectasis and sinusitis with situs inversus, the respiratory tract pathology having been found in approximately 20 per cent of the cases of transposition.<sup>4, 22, 23, 24</sup> It has been suggested that situs inversus may be caused by one of two mechanisms: one form is genetically determined and carries with it no liability (the concept that situs inversus is inherited as a Mendelian recessive character finds statistical support in Cockayne's studies<sup>21</sup>); the other form is the result of maldevelopment on the basis of an unfavorable intrauterine environment, under which conditions other congenital abnormalities might occur in addition to visceral transposition.<sup>4</sup>

We have been able to find in the literature a total of 15 cases of acquired heart disease associated with congenital dextrocardia and situs inversus. These include: rheumatic heart disease, three cases (one case of mitral stenosis<sup>25</sup> and two cases of combined mitral and aortic lesions<sup>26, 19</sup>); two cases of syphilitic

aortitis<sup>24, 27</sup>; and one case of calcareous aortic stenosis<sup>20</sup>; one case of chronic cor pulmonale<sup>28</sup>; one case which from the clinical evidence presented is strongly suggestive of thyrotoxic heart disease, although no etiologic diagnosis is made in the case report<sup>29</sup>; two cases of hypertensive heart disease<sup>30, 31</sup>; one case of combined hypertensive and coronary heart disease<sup>7</sup>; and four cases of coronary heart disease.<sup>32, 33, 3, 6</sup> In five of the 15 cases symptoms of angina pectoris or myocardial infarction were present; in three of the cases the pain was in the right chest or radiated only to the right arm<sup>6, 24, 33</sup>; in one case<sup>7</sup> it was in the left chest, and

TABLE I  
Incidence of Congenital Dextrocardia

Number of Cases of Congenital Dextrocardia Found	Number of Individuals Examined	Nature of Examination	Incidence Frequency	%	Author
		Military service (physical examination)	1:35,000	.0029	LeWald <sup>1</sup>
14	124,830	Autopsy (consecutive)	1:8920	.011	German autopsy records, cited by Cockayne <sup>21</sup>
23	232,112	Consecutive hospital patients	1:10,090	.0099	Adams and Churchill <sup>4</sup>
15	180,000	Military service (x-ray)	1:12,000	.0083	Geeslin and Tyler <sup>3</sup>
8	100,000	Military service (x-ray)	1:12,500	.0080	Caplan <sup>2</sup>
36	223,182	Military service (x-ray)	1:6200	.016	Morse <sup>5</sup>
6	36,717	Mass x-ray survey	1:6120	.016	Russakoff and Katz <sup>41</sup>
40	442,252	Mass x-ray survey	1:11,060	.0091	Gould <sup>43</sup>
6	37,257	Mass x-ray survey	1:6210	.016	Robins and Ehrlich <sup>44</sup>
Total 148	1,376,350		1:9300	.0108	

In several instances above, a clear-cut distinction between the two forms of congenital dextrocardia, namely isolated dextrocardia and that occurring as part of a general visceral transposition, has not been made. Since, however, the former anomaly is much rarer than the latter<sup>45, 46, 47</sup>, the incidence of situs inversus is probably not significantly lower than the average figure derived from the total.

In the remaining case<sup>3</sup> the pain was in mid-chest and radiated to both arms. In our patient the pain was in the right chest and radiated to both arms. It is apparent from the five cases in the literature and from the case reported above, that in congenital dextrocardia the pain associated with myocardial anoxia tends to be referred to the side of the body on which the organ is situated; but this is not invariable as indeed is the case in sinistocardia, where anginal radiation tends to be to the left, but may be to both sides, or only to the right.<sup>34</sup> King<sup>24</sup> discussing reference of pain in cases of visceral transposition suggests that con-

tralateral reference may be a result of the failure of the nervous pathways to share in the general visceral rotation.

We have been unable to find a case report in the literature of hiatus hernia in association with congenital dextrocardia and situs inversus. Acquired dextrocardia caused by displacement of a previously normally situated heart by the presence of abdominal viscera in the left chest as a result of a diaphragmatic hernia is not uncommon; indeed, since diaphragmatic hernia occurs much more commonly on the left than on the right, the condition is one of the common causes of acquired dextrocardia.<sup>35</sup>

In the past decade increased recognition has been accorded to the fact that hiatus hernia may produce chest pain very similar to the anginal syndrome associated with coronary heart disease.<sup>8, 9, 12, 36</sup> Since symptoms associated with hiatus hernia tend to occur in those age groups in which coronary and hypertensive heart disease show their highest frequency the lesions frequently coexist; in Jones' <sup>12</sup> series of 128 cases of hiatus hernia there were 13 individuals who also had heart disease, while Ohler and Ritvo <sup>13</sup> found probable heart disease in six of their 104 cases. There can be no doubt that many hernias are asymptomatic and are detected as incidental findings in a gastrointestinal series.<sup>13, 37, 38</sup> On the other hand, it is true that in many cases of heart disease with angina pectoris there are no significant resting electrocardiographic abnormalities<sup>39</sup> nor other obvious objective manifestations of the disorder. In a case of chest pain in which a hiatus hernia is demonstrated, the possibility that coronary heart disease is present should always be considered. As Moschcowitz <sup>40</sup> pointed out, precise diagnosis and definitive treatment demand a differentiation of the cause of the pain and ascribing it to one or the other cause or possibly both. Much has been written emphasizing the error of making a diagnosis of coronary heart disease in cases where the symptomatology is actually due to hiatus hernia <sup>8, 14, 40</sup>; however, the possibility of overlooking a true angina pectoris in the presence of an asymptomatic hiatus hernia has not been equally stressed. From careful clinical appraisal of the symptomatology, electrocardiograms, roentgen-ray, the response to treatment with parasympatholytic or antispasmodic drugs, bland diet and coronary vasodilators, in most cases a precise diagnosis may be made, with evaluation of the contribution of each lesion to the symptoms.

#### SUMMARY

1. An unusual case of congenital dextrocardia with situs inversus associated with coronary heart disease, angina pectoris and hiatus hernia is presented. This is the first such case to be reported.
2. The literature relating to the incidence of congenital dextrocardia is reviewed. The anomaly has an incidence of about 0.01 per cent.
3. Case reports in the literature on situs inversus associated with acquired heart disease are reviewed.
4. The need for careful differentiation of coronary heart disease from hiatus hernia as a cause of chest pain is emphasized.

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## ELECTROCARDIOGRAPHIC EVIDENCE OF RIGHT AND LEFT ANTERIOR WALL INJURY DUE TO GUNSHOT WOUND OF THE HEART \*

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SINCE gunshot and stab wounds of the heart produce localized myocardial lesions, they are of considerable clinical importance in the interpretation of electrocardiographic changes. No other myocardial disease demonstrates localization so well, and similar lesions can be produced only by direct, localized experimental injuries of the myocardium in animals. In both gunshot and stab wounds, during the first two weeks, the electrocardiogram shows predominantly

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changes associated with pericarditis. There have been few case reports with permanent electrocardiographic evidence of injury of the right or left ventricle.<sup>1</sup>

Cases with electrocardiographic evidence of post-traumatic left anterior wall infarction or injury are usually the result of laceration, severance, or operative



FIG 1. Roentgenogram, posterior-anterior view. A metallic fragment is seen at the border between right and left ventricle below the level of the aortic valve

ligation of the anterior descending branch of the left coronary artery. Q-waves and T-wave inversions are found in Leads I and IV. Cases of right ventricular injury often develop transient or permanent right bundle-branch block.<sup>2</sup> T-wave changes and occasionally small Q-waves have been present in Leads II and III

or in all three leads.<sup>1, 2</sup> No definite electrocardiographic pattern of right ventricular injury has been established in human beings, since isolated myocardial infarction of this region never occurs.

The following case of gunshot wound of the heart is presented because of the



FIG. 2. Left lateral view: The projectile is seen to be anteriorly within the myocardium.

characteristic electrocardiographic findings which made it possible to localize the injury to the anterior wall of the right and left ventricle. This interpretation was corroborated by the roentgenological localization of the shrapnel fragment which caused the injury.

## CASE REPORT

A 23 year old World War II veteran was referred to the Cardiac Section of the Veterans Hospital, Bronx, New York, for consultation. While on active duty in Belgium as a gunner with an anti-tank outfit, the patient was wounded by a high explosive shell in September, 1944. Numerous shrapnel fragments penetrated deeply into the soft tissues of his left leg, hand, arm, neck, face, and chest. At no time did he lose consciousness, although he bled profusely. An operation was performed in a field hospital, where one fragment was removed from the pericardium through an anterior chest wound to the left of the sternum. Another fragment was seen in the myocardium but was not removed. Traveling in an air ambulance from Paris to England nine days later he developed marked dyspnea. He was admitted to a hospital in England and was kept in an oxygen tent for some time with gradual and progressive disappearance of his symptoms. An abscess of the anterior chest wall had formed, and this was incised and drained with complete healing. Roentgen-ray examinations of the chest in October 1944, revealed a moderate left pleural effusion and a metallic foreign body within the anterior wall of the heart, probably in the right ventricle. On fluoroscopy this metal fragment was seen to pulsate vigorously. A contemplated operation for its removal was deferred because of the onset of repeated attacks of severe, stabbing, precordial pain associated with moderate dyspnea on exertion. During the next few months these attacks gradually decreased in frequency. In March, 1945, he was transferred to Valley Forge General Hospital and a few months later to Ashford General Hospital for further evaluation of his cardiac status. He was finally discharged from Walter Reed Hospital. Although surgical removal was considered at various times, it was thought to be more dangerous than the remote possibility that the foreign body would penetrate to the endocardial surface, be embolized, or be the site of bacterial endocarditis. Although cardiac neurosis was regarded as the most likely cause of the paroxysmal angina pectoris and dyspnea, nevertheless its organic origin could not be definitely excluded.

At the present time the patient complains of frequent pain in his numerous scars, particularly in his left hand, where extensive plastic surgery has been done. He often experiences a heavy feeling and tightness in his chest, mild precordial pain, and dyspnea after walking only two flights of stairs. He has had no complaints of cough or expectoration and never developed edema of his lower extremities.

*Physical Examination.* The patient was well built and nourished, and appeared in no acute distress or discomfort. There were multiple scars due to gunshot wounds and plastic surgery on the left anterior chest, left arm, forearm, wrists, hand and right shoulder. There was one postoperative scar six and one-half inches in length extending from the left sternal margin to the anterior axillary line at the level of the third intercostal space. Cyanosis, edema, and clubbing were not present. The apical impulse was felt within the midclavicular line. No abnormal pulsations or thrills were noted. The heart sounds were of good quality. There were no murmurs or friction rub. Examination of the lungs and abdomen revealed no abnormality. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic in both arms.

*Electrocardiographic Examinations.* The conventional electrocardiogram revealed the following: Regular sinus rhythm, tendency to right axis deviation, deep Q-waves in Leads II, III, CF<sub>2</sub>, CF<sub>3</sub> and CF<sub>4</sub>. The T-waves were inverted in CF<sub>3</sub> and CF<sub>4</sub>, low in CF<sub>2</sub> and iso-electric in CF<sub>6</sub>.

Augmented unipolar extremity leads revealed a deep Q-wave in aV<sub>F</sub>, a slight depression of the ST-segment in aV<sub>L</sub>, and inversion of the T-wave in aV<sub>L</sub>. Multiple chest leads recorded with a unipolar central terminal revealed deep Q-waves in V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub>, and small Q-waves in V<sub>5</sub> and V<sub>6</sub>. The T-wave was semi-inverted in V<sub>5</sub> and inverted in V<sub>4</sub>.

These changes ordinarily would have been interpreted as indicating a previous anterior and posterior wall infarction or injury. Knowing, however, that the myocardial trauma had occurred only anteriorly, they were regarded as diagnostic of right and left anterior wall injury.

*Roentgenographic and Fluoroscopic Examination.* Radiographic examination of the chest in various positions revealed a metallic fragment 14 by 8 by 6 mm. anteriorly, at the border of the right and left ventricle and somewhat below the level of the aortic valve. Fluoroscopy revealed it to be deep within the myocardium and to pulsate vigorously with cardiac contractions. Several additional metal fragments were seen within the left chest. The left clavicle showed evidence of an old healed fracture.



FIG. 3. Left anterior oblique view: The shrapnel fragment is seen well within the cardiac shadow.

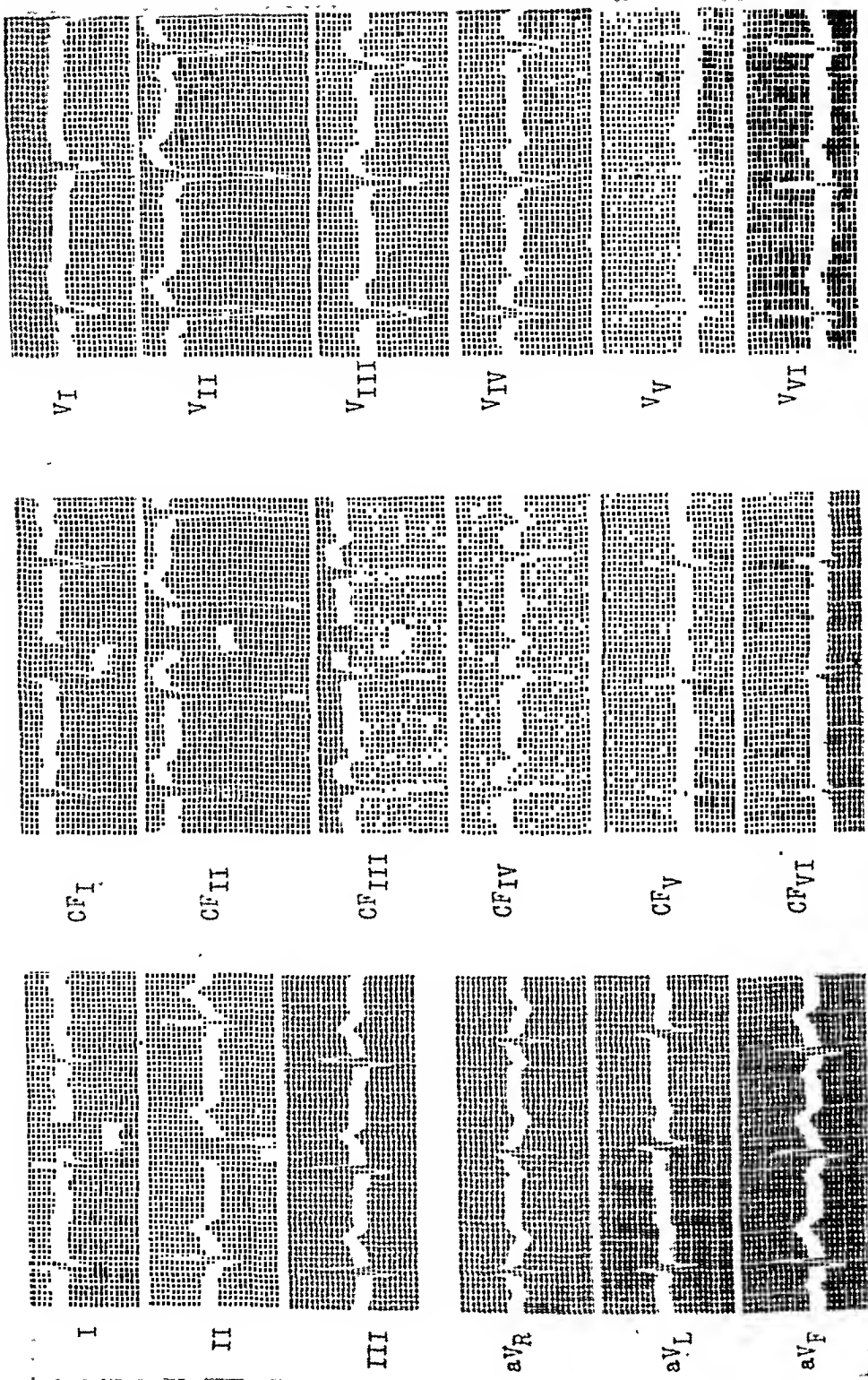


FIG. 4. The electrocardiogram shows evidence of right and left anterior wall injury: Deep Q-waves are present in Leads II and III, CF I, CF II, CF III, CF IV, CF V, and CF VI.

## COMMENT

Case reports of stab or gunshot wounds of the heart with electrocardiographic evidence of left anterior wall injury have not been rare.<sup>2</sup> However, in our opinion none has been observed with well defined electrocardiographic evidence of right anterior ventricular wall injury. The myocardial infarction encountered in acute coronary occlusion rarely involves the wall of the right ventricle. Electrocardiographic findings of right ventricular infarction have thus far not been described from clinical observations. In the experimental animal, right ventricular injury of the anterior as well as diaphragmatic surface results in the development of Q-waves, R-ST segment elevations and subsequent T-wave changes similar to those seen in left posterior wall infarction.<sup>3</sup> Therefore a deep Q-wave in Leads II and III, elevations of the RST segments in Leads II and III, and T<sub>2</sub> and T<sub>3</sub> inversion are found in left posterior wall infarction as well as right ventricular infarction or injury. In our case no injury of the left posterior surface occurred, as the fragment entered through the anterior chest wall. Pericarditis, pericardial effusion, or adhesions are known not to result in Q-waves. The metallic foreign body as seen roentgenographically gives the exact site of the myocardial injury: anterior surface of the heart involving the left and right anterior wall. Since it is deep within the myocardium, one can reasonably assume that it caused extensive necrosis and subsequently scar tissue. Because of this we feel that the electrocardiographic findings are those of right and left anterior wall injury.

Surgeons who have had considerable war experience with gunshot wounds of the heart are of the opinion that metallic fragments should be removed under all circumstances because of possible complications.<sup>4,5</sup> Delivery into the ventricular cavity with peripheral embolization may occur at any time, soon after the injury or years later. Aneurysm of the involved ventricle may develop and subacute bacterial endocarditis may occur at the site of the projectile, walled off by connective tissue. Constrictive pericarditis due to an unremoved foreign body from the pericardium has been observed.<sup>6</sup> Pressure on the cardiac nerve plexus may cause angina pectoris, completely relieved by removal of the projectile.<sup>7</sup> While the electrocardiogram may be of considerable help in the localization of the cardiac injury in gunshot wounds, its usefulness for operative indication appears limited. The cases reported and our own experience do not allow us to draw any conclusions in this respect. Cases with persistent electrocardiographic findings due to an unremoved shrapnel or projectile may be perfectly asymptomatic, while others with complete electrocardiographic recovery may show signs and symptoms of cardiac embarrassment. Evaluation of the danger involved in removal of the fragment, as against the remote danger of future complications, should be the only guide.<sup>8</sup>

## SUMMARY

A case of gunshot wound of the heart involving the right and left anterior ventricular surfaces is presented. The site of the cardiac injury is demonstrated roentgenographically by an unremoved metallic fragment. Electrocardiographic findings characteristic of right and left anterior wall injury are shown in this case. The possible complications due to unremoved foreign body from the heart

are discussed. The limitations of the electrocardiogram as an indication for surgical intervention are briefly indicated.

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## EDITORIAL

### BIOLOGICAL COMPETITION BETWEEN STRUCTURALLY RELATED COMPOUNDS: CLINICAL IMPLICATIONS

THE introduction in 1935 of the sulfonamide group of drugs<sup>1</sup> opened a new era of chemotherapeutic endeavor. In 1940 the publication of the Woods-Fildes theory<sup>2</sup> provided not only a satisfactory explanation of the mode of action of these drugs but also a highly important basis for a rational extension of chemotherapeutic research. The basis of the theory was the principle of the biological competition of structurally related compounds. The para-amino benzoic acid-sulfonamide relationship admirably exemplifies this concept.

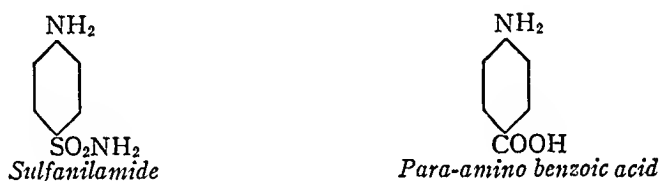


FIG. 1.

Woods reported that yeast extracts contained a substance which reversed the inhibitory action of sulfanilamide on the growth of hemolytic streptococci. This substance was identified with para-amino benzoic acid and attention was called to the chemical similarity of the drug to this compound (figure 1). Para-amino benzoic acid was considered to be an essential metabolite for hemolytic streptococci, and the effectiveness of sulfanilamide in producing bacteriostasis was thought to be directly related to the structural similarity between the two. Fildes<sup>3</sup> had defined an essential metabolite as an organic substance without which metabolism cannot proceed to the extent required by growth. Under normal circumstances of bacterial growth, PABA was utilized by some intracellular enzyme system. It was suggested that the structural analogue (sulfanilamide) competitively displaced the normal metabolite, thereby interfering with some normal enzymic function with resultant bacteriostasis. Subsequently, PABA was recognized as a factor essential for the growth of a number of bacterial species<sup>4</sup> and was included in the vitamin B complex.

<sup>1</sup> DOMAGK, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, *Deutsch. med. Wchnschr.*, 1935, lxi, 250.

<sup>2</sup> WOODS, D. D.: The relation of p-amino benzoic acid to the mechanism of action of sulphanilamide, *Brit. Jr. Exper. Path.*, 1940, xxi, 74.

<sup>3</sup> FILDES, P.: The mechanism of the anti-bacterial action of mercury, *Brit. Jr. Exper. Path.*, 1940, xxi, 67.

<sup>4</sup> RUBBO, S. D., and GILLESPIE, J. M.: Para-amino benzoic acid as a bacterial growth factor, *Nature*, 1940, cxlvi, 838.

The nature of the cellular metabolic mechanism involved in this competitive reaction was unknown at the time of Woods' studies. The discovery of the structure and synthesis of folic acid in 1946<sup>5</sup> shed additional light upon this problem. Folic acid was found to consist of para-amino benzoic acid, glutamic acid and the pterin ring. It now seems established beyond reasonable doubt that the sulfonamides prevent the synthesis of folic acid through their interference with the incorporation of para-amino benzoic acid in the folic acid molecule.<sup>6</sup> Since the latter is essential for the growth of many bacteria, interference with its formation leads to bacteriostasis. Microorganisms which are entirely independent of the need for folic acid are not sensitive to sulfonamides. Bacteria which require ready-made folic acid as a growth factor are also insensitive to the sulfonamides, since they lack the metabolic step upon which the drug acts. On the other hand, sulfonamide-sensitive organisms are those which must form their own folic acid from para-amino benzoic acid. Evidence has recently accumulated which extends our information even somewhat further regarding the rôle of folic acid in cellular metabolism. In a manner not yet elucidated, it appears that folic acid is concerned in intracellular syntheses of amino acids, purines and pyrimidines.<sup>7</sup>

The basic concept of the biological antagonism of structurally related compounds has been subjected to additional investigation, with some very striking results. Wooley and White<sup>8</sup> fed mice an analogue of thiamine, pyriethamine and were able to produce signs of a severe thiamine avitaminosis which could be reversed by feeding the vitamin. Signs of scurvy were induced in mice and guinea pigs by the feeding of gluco-ascorbic acid, an analogue of ascorbic acid.<sup>9</sup> These changes could also be reversed by feeding the vitamin. Pyridoxine deficiency has been induced in chickens by feeding the analogue, desoxypyridoxine.<sup>10</sup> Numerous additional examples could be cited.

It is worth while here to stress briefly a fundamental principle in this competitive phenomenon. The effect of an antagonist is dependent not upon the absolute amount used but rather upon the ratio of the quantity of analogue to that of metabolite.<sup>11</sup> This ratio is expressed in terms of a so-

<sup>5</sup> ANGIER, R. B., BOOTH, J. H., HUTCHINGS, G. L., MOWAT, J. H., SEMB, J., STOKSTAD, E. L. R., SUBBA ROW, Y., WALLER, C. W., COSULICH, D. B., FAHRENBACH, M. J., HULTQUIST, M. E., KUH, E., NORTHEY, E. H., SEEGER, D. R., SICKELS, J. P., and SMITH, J. M.: The structure and synthesis of liver, *L. casei* factor, *Science*, 1946, ciii, 667.

<sup>6</sup> LAMPEN, J. O., and JONES, M. J.: Antagonism of sulfonamide inhibition of certain lactobacilli and enterococci by pteroyl-glutamic acid and related compounds, *Jr. Biol. Chem.*, 1946, clxvi, 435.

<sup>7</sup> LAMPEN, J. O., ROEPKE, R. R., and JONES, M. J.: The replacement of p-amino-benzoic acid in the growth of a mutant strain of *E. coli*, *Jr. Biol. Chem.*, 1946, clxiv, 789.

<sup>8</sup> WOOLEY, D. W., and WHITE, A. G. C.: Production of thiamin deficiency disease by feeding of a pyridine analogue of thiamin, *Jr. Biol. Chem.*, 1943, 285.

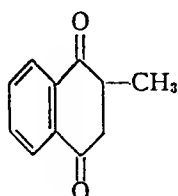
<sup>9</sup> WOOLEY, D. W., and KRAMPITZ, L. O.: Production of a scurvy-like condition by feeding of a compound structurally related to ascorbic acid, *Jr. Exper. Med.*, 1943, lxxviii, 333.

<sup>10</sup> OTT, W. H.: Antipyrindoxine activity of 2, 4-dimethyl-3-hydroxy-5-hydroxymethyl-pyridine in the chick, *Proc. Soc. Exper. Biol. and Med.*, 1946, lxi, 125.

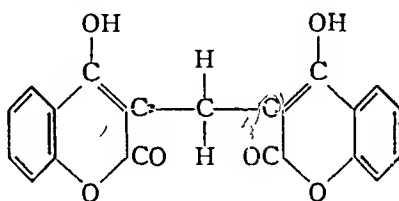
<sup>11</sup> WOOLEY, D. W.: Recent advances in the study of biological competition between structurally related compounds, *Physiol. Rev.*, 1947, xxvii, 308.

called inhibition index. The inhibition index is usually greater than one, i.e. proportionately smaller quantities of metabolite are required to reverse the inhibition induced by an analogue. This may be due to a greater natural affinity of the cellular enzyme for the metabolite.

The phenomenon of biological competition of structurally related compounds has many implications. Used as biochemical tools, inhibitory structural analogues, by specifically interfering with a metabolic process, may help to elucidate phases of intermediate metabolism previously unknown. The developments based upon the PABA-sulfonamide antagonism offer an excellent example of this. Furthermore, the utilization of varied analogues of the same metabolite may cast additional light upon varied functions of the latter. The regulation of certain metabolic activities by pairs of normally occurring structural analogues has been postulated. The estrogen-androgen relationship may be mentioned in this connection.<sup>12</sup>



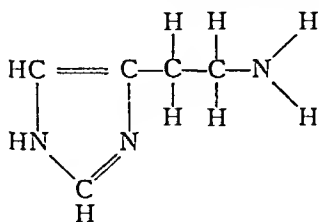
*Synthetic Vitamin K (Menadione)*



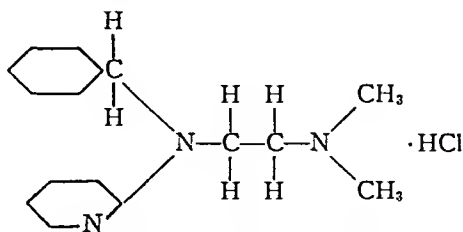
*Dicoumarol*

FIG. 2.

From the standpoint of the clinician, an extremely important aspect of this concept is its influence upon chemotherapeutic research. In retrospect, the mode of action of several important drug groups can probably be explained by this phenomenon. As illustrations, one can cite the vitamin K-dicoumarol relationship as well as the recent spectacular applications of the anti-histaminic drugs. In the case of the former, the basic similarity of the chemical constitution of these two agents was pointed out by Witts<sup>13</sup> (figure 2), and the suggestion made that dicoumarol exerts its effect by



*Histamine*



*Pyribenzamine Hydrochloride*

FIG. 3.

interfering with the utilization of vitamin K by the liver. Like histamine, most of the effective anti-histaminic drugs are derivatives of ethylamine (figure 3) and are believed to be effective because of competition with the

<sup>12</sup> WOOLEY, D. W.: Biological antagonisms between structurally related compounds, *Advances in Enzymology*, 1946, vi, 129.

<sup>13</sup> WITTS, L. J.: Disturbances in coagulation of blood, *Glasgow Med. Jr.*, 1942, cxxxvii, 57.

former for attachment to specific cell receptors.<sup>14</sup> Recent trials of a group of folic acid antagonists, notably aminopterin, in the therapy of acute leukemia represent a further extension of this chemotherapeutic principle.<sup>15, 16</sup>

As a result of recent developments, based upon this concept, the narrow view of chemotherapy as the treatment of infectious diseases with chemical agents would no longer seem to be tenable. Chemotherapeutic agents which may produce bacteriostasis by interference with bacterial nutrition have been found to have a profound effect upon cellular metabolism in the animal body. In many instances there is striking similarity between the metabolic processes of bacteria and higher animals. The close interrelation of bacterial and animal nutrition is well exemplified in the rapid translation of the recently acquired knowledge of the nutritional requirement of *Lactobacillus casei* for folic acid and *Lactobacillus lactis* Dorner for vitamin B<sub>12</sub>, to the therapy of human disease. Although most studies in this field during recent years have been concerned with the antagonism of essential metabolites by a variety of their structural analogues, the principle has already been extended to include materials other than essential metabolites. The problems which beset the experimentalist in this field are numerous and varied. Synthesis of analogues obviously requires prior knowledge of the structure of essential metabolites, many of which are still unknown. Many analogues, when synthesized, will have no clinical value because of toxicity. Although many brilliant chemotherapeutic successes of the past have been achieved empirically, there is reason to believe that the continued application of the principle of competitive antagonism of structurally related compounds will not only stimulate but expand the horizons of chemotherapy in its broadest sense.

MILTON S. SACKS

<sup>14</sup> KRANTZ, J. C., JR., and CARR, C. J.: The pharmacologic principles of medical practice, 1949, Baltimore, p. 679.

<sup>15</sup> FARBER, S., DIAMOND, L. K., MERCER, R. D., SYLVESTER, R. F., JR., and WOLFF, J. A.: Temporary remissions in acute leukemia in children produced by a folic acid antagonist, 4-amino pteroyl glutamic acid (aminopterin), New England Jr. Med., 1948, ccxxxviii, 787.

<sup>16</sup> SACKS, M. S., and BRADFORD, G.: Unpublished observations.

## REVIEWS

*Diseases of the Fundus Oculi with Atlas.* By ADALBERT FUCHS, M.D., e.o. Professor of Ophthalmology of the University of Vienna. Translated by ERICH PRESSBURGER, M.D.; Edited by ABRAHAM SCHLOSSMAN, M.D. First English edition, limited to 995 numbered copies. 337 pages (plus 44 pages illustrations in color); 19 × 27.5 cm. The Blakiston Co., Philadelphia. 1949. Price, \$30.00.

This handsomely bound volume, printed in limited edition, is based on the lecture courses on fundus disease which have been delivered by the author over the past 25 years, and was first published in German in 1943. The present edition contains a few additions to both the text and the illustrations of the previous issues. The book is an attempt to combine in one volume both a textbook and atlas of ophthalmoscopy.

As an atlas this book bears sad testimony to the decline of the printing art during the past generation. The height of the art as exemplified in ophthalmoscopic atlases was reached in the production of Oeller issued in successive fascicules over the years 1895 to 1924. These meticulous drawings, reproduced in marvelous perfection by the European printers, were for two generations the standard wall decorations of the lecture rooms of departments of ophthalmology in various European universities. Their accuracy is such that it is still possible, after all these years and in the light of more modern knowledge, to make new and more refined diagnoses on the cases presented.

The best modern atlas of ophthalmoscopy from the reproductive point of view is, unquestionably that of Wilmer, printed by Hoen in 1934. In accuracy of drawing and of reproduction, Wilmer's atlas is fully equal to that of Oeller, falling short only in the number of conditions portrayed. The illustrations of the Fuchs book are evidently based on drawings of very fine quality, but their reproduction in small scale and in somewhat garish colors leaves much to be desired.

The text also falls short of the desiderata in respect to a modern textbook of ophthalmoscopy. It is less complete and less imbued with modern medical teaching than, for instance, the "Diseases of the Retina" recently published by Elwyn. In fact, the medical literature of the last 20 years is hardly mentioned. Nevertheless, the combination of atlas and textbook has a merit of its own, and the amplification of the fundus drawings by illustrations, also, of the histological pictures in typical cases adds much to the value of the book.

Those ophthalmologists who were suckled in their professional training on the classical textbook of Ernst Fuchs, father of the present author, will find additional nostalgic value in the frequent references to the subsequent histories in some of the illustrative cases originally cited by the elder Fuchs.

JONAS FRIEDENWALD

*Internal Medicine in General Practice.* 2nd Ed. By ROBERT PRATT McCOMBS, B.S., M.D., F.A.C.P., Director of Postgraduate Teaching, Tufts College Medical School. 741 pages, 16.5 × 24.5 cm. W. B. Saunders Company, Philadelphia. 1947. Price, \$8.00.

This second edition continues like the first edition in the Osler tradition and integrates the major facets of Internal Medicine through the eyes of one man. In places it may seem somewhat oversimplified. But it is factual, concise, and the chapters are readable without being exhausting. Sections on psychiatry and peripheral vascular disease have been added. There are eight more pictures and 52 more pages. Otherwise it remains essentially the same in format and spirit. The initial

chapter on "Fundamentals of Diagnosis" still makes a good introduction to clinical medicine for students.

Some charts (cf. table 3) seem unduly elaborate and space wasting. One wonders why, in so compact a presentation, a large illustration of the Westergren apparatus is thought necessary, and why if one *technic* is detailed, the Wintrobe and others are not mentioned. The aerosol illustration similarly seems out of place here, though doubtless cuts of smaller models were not available then.

Chemotherapy is conservatively dealt with, though therapeutic testing is rather frequently suggested. Chemotherapy in "the mildly ill" is warned against and abandonment in any case if ineffective after 72 hours is properly emphasized.

Newer antitussics are available, so the occasional recommendation of "morphine or codein" for cough, without suggestion of less habit forming drugs may be disliked by some readers.

Some acknowledgment should be made of disease variability with climate and geography. For instance, virus pneumonia is "highly contagious" with "complications unusual." This is in line with Longcope's early report concerned with cases in the Middle Atlantic Region. In other areas, notably Hawaii, where the condition was probably first reported, it is not considered particularly contagious. A variety of complications has been reported, pleurisy, sterile abscesses, and bronchiectasis.

These exceptions are all relatively minor. The many good points far outweigh the few bad ones. The text continues to be a welcome, fresh approach in a field replete with older, overgrown, cumbersome books. It is a good review and point of occasional reference for general practitioner and specialist as well. It can be recommended to the intelligent layman for exposition of a modern point of view on internal medicine.

C. B. A.

*Experimental Immunochemistry.* By ELVIN A. KABAT, Ph.D., and MANFRED M. MAYER, Ph.D., with a Foreword by MICHAEL HEIDELBERGER, Ph.D. 575 pages; 24 x 15.5 cm. 1948. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$8.75.

One of the greatest deterrents to the increase of knowledge in medical sciences today is the progressive specialization of the individual disciplines. Any book which makes even a partial try at bridging the gap between two branches is likely to be worthwhile. This book is successful in presenting to the chemist the ideas and practices of the immunologist, and in presenting immunological facts to the chemist. It is written by two competent students of Heidelberger, the outstanding leader in this country in the field of immunochemistry.

The book has some theoretical discussion throughout, but it is mainly one for use in the laboratory. Part I: Immunological and Immunochemical Methodology; Part II: Applications and Uses of Quantitative Immunochemical Methods; Part III: Chemical and Physical Methods; and Part IV: Preparations, are the titles of the four main parts and are sufficient reason for Heidelberger's statement in the Preview that "the book is, therefore, more likely to gather acid spots and indicator stains on the laboratory table than to accumulate dust on the reference shelves."

It is too bad, then, that the laboratory worker will have to squint his eyes hard and long to read some of the very fine print in the tables throughout.

This is a book of great value to all experimental workers in infectious diseases, allergy and biochemistry.

F. B. B.

*Advances in Pediatrics.* Volume 3. Editorial Board: S. Z. LEVINE, ALLAN M. BUTLER, L. EMMETT HOLT, JR., and A. ASHLEY WEECH. 363 pages; 16 × 24 cm. Interscience Publishers, Inc., New York 3, N. Y. 1948. Price, \$7.50.

This is the third volume of a personalized monographic presentation of pediatric subjects of current interest. The topics are written by authorities in their respective fields. The present issue contains eight monographs. Those by Dr. Milton Senn, "Emotions and Symptoms in Pediatric Practice," and Dr. Hilde Bruch, "Puberty and Adolescence: Psychologic Considerations," are representative of current pediatric thinking. The articles are well organized and offer physicians an opportunity to keep abreast of pediatric progress.

J. E. B.

*Gardiner's Handbook of Skin Diseases.* Revised by JOHN KINNEAR, O.B.E., T.D., M.D., M.R.C.P. (Ed.). 250 pages; 13 × 19.5 cm. The Williams and Wilkins Company, Baltimore. 1948. Price, \$4.50.

The author has presented a small, well written text which he has illustrated with a number of excellent black and white photographs and color plates. As stated in the preface this is a handbook and is not intended to replace a larger text. It deals adequately with the commoner skin diseases and briefly mentions some of the rarer ones. There are some minor variations between the terminology used in this book and those in common usage in the United States and some of the therapeutic suggestions are seldom followed in this country. Unfortunately, the author has not stressed the importance of the dark field examination as the most important diagnostic procedure in early syphilis, but rather stresses the convenience of the serologic test for syphilis. The chapters on fungus diseases are adequate. There is an interesting and practical chapter on the toxic dermatoses, under which heading the author also discusses eczema. The text is recommended for use by the general practitioner, and also by the student. It contains much valuable information in condensed form.

H. M. R.

*Dr. W. C. Röntgen.* By OTTO GLASSER, Cleveland Clinic Foundation. 169 pages; 14.5 × 22 cm. Charles C. Thomas, Springfield. 1945. Price, \$4.50.

Commemorating the fiftieth anniversary of the first report describing x-rays, Dr. Otto Glasser has composed a small volume retelling the story of their discovery. The identification of x-rays by W. C. Röntgen has often been described in a sensational fashion. Much to the credit of the author, the events prior to their discovery are related in a simple style.

Little known scientific studies of Professor Röntgen are discussed and serve to broaden our admiration for this pure scientist. He apparently was well known among the German universities for his investigations in the properties of gases. It was not until after 1890 that he became interested in a new tool, the cathode ray tube. This small biography describes in detail the original work leading up to the demonstration of an unknown ray and the following studies of this ray. His first and subsequent reports are reprinted. These are of twofold interest: The physical principles as then known are described in these reports.

Many glimpses are afforded of the man, Röntgen. Doubtlessly, few of us today would have refused the easy offers that were made to secure nobility and a comfortable fortune, largely tax free. He had very human traits, since he served on several faculties, moving from one to the other depending on which university offered the best research facilities.

This biography should be required reading for roentgenologists. They would,

perhaps, complain less of their present equipment if they compared their "plight" to the technical problems faced by Professor Röntgen.

D. J. B.

### BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Aviation Medicine in Its Preventive Aspects: An Historical Survey.* By JOHN F. FULTON, O.B.E., M.D., D.Sc., Sterling Professor of Physiology, Yale University. 174 pages; 22.5 × 14.5 cm. 1949. Oxford University Press, New York. Price, \$3.50.

*Child Psychiatry.* 2nd Ed. By LEO KANNER, M.D., Associate Professor of Psychiatry, The Johns Hopkins University, etc.; with Prefaces by JOHN C. WHITEHORN, M.D., Henry Phipps Professor of Psychiatry, The Johns Hopkins University; ADOLF MEYER, M.D., LL.D., Henry Phipps Professor Emeritus of Psychiatry, The Johns Hopkins University, and EDWARD A. PARK, M.D., Professor Emeritus of Pediatrics, The Johns Hopkins University. 752 pages; 26.5 × 16 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$8.50.

*Clinical Case-Taking: Guides for the Study of Patients; History-Taking and Physical Examination or Semiology of Disease in the Various Systems.* 4th Ed. By GEORGE R. HERRMANN, M.D., Ph.D., Professor of Medicine, University of Texas. 240 pages; 22.5 × 14.5 cm. 1949. The C. V. Mosby Company, Saint Louis. Price, \$3.50.

*Diabetes and Its Treatment.* By JOSEPH H. BARACH, M.D., F.A.C.P., Associate Professor Medicine, University of Pittsburgh, etc. 326 pages; 24.5 × 16.5 cm. 1949. Oxford University Press, New York. Price, \$10.00.

*Diabetic Menus, Meals and Recipes.* By BETTY M. WEST; Introduction by RUSSELL F. RYPINS, M.D., Chief, Diabetic Clinic, Mt. Zion Hospital, San Francisco. 254 pages; 22 × 14.5 cm. 1949. Doubleday & Company, New York. Price, \$2.95.

*Diseases of the Fundus Oculi with Atlas—First English Edition (Limited Edition of 995 numbered copies).* By ADALBERT FUCHS, M.D., e.o. Professor of Ophthalmology, University of Vienna; Translated by ERICH PRESSBURGER, M.D.; Edited by ABRAHAM SCHLOSSMAN, M.D. 337 pages, plus 44 pp. illus. in color; 27.5 × 19 cm. 1949. The Blakiston Company, Philadelphia. Price, \$30.00.

*Doctors of Infamy: The Story of the Nazi Medical Crimes.* By ALEXANDER MITSCHERLICH, M.D., Head of the German Medical Commission to Military Tribunal No. 1, Nuremberg; Translated by HEINZ NORDEN; with Statements by Three American Authorities Identified with the Nuremberg Medical Trial: ANDREW C. IVY, M.D., Vice-President, University of Illinois, etc.; TELFORD TAYLOR, Brigadier General, U. S. Army, Chief of Counsel for War Crimes; and LEO ALEXANDER, M.D., Psychiatrist, Consultant to the Secretary of War and to the Chief of Counsel for War Crimes; and a Note on Medical Ethics by ALBERT DEUTSCH (Including the New Hippocratic Oath of the World Medical Association); 172 pages; 21.5 × 14.5 cm. 1949. Henry Schuman, Publisher, New York. Price, \$3.00.



- An Elementary Atlas of Cardiography: An Introduction to Electrocardiography and X-ray Examination of the Heart.\** By H. WALLACE-JONES, M.D., M.Sc., F.R.C.P., Honorary Consulting Physician, Royal Liverpool United Hospital; E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., Honorary Physician, Royal Liverpool United Hospital, and E. L. RUBIN, M.D., F.F.R., D.M.R.E., Honorary Radiologist, Royal Liverpool United Hospital. 108 pages; 23 × 14.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$3.00.
- Industrial Fluorosis: A Study of the Hazard to Man and Animals near Fort William, Scotland. Medical Research Council Memorandum No. 22.* A Report to the Fluorosis Committee by JOHN N. AGATE, G. H. BELL, G. F. BODDIE, R. G. BOWLER, MONAMY BUCKELL, E. A. CHEESEMAN, T. H. J. DOUGLAS, H. A. DRUETT, JESSIE GARRAD, DONALD HUNTER, K. M. A. PERRY, J. D. RICHARDSON and J. B. DE V. WEIR. 131 pages; 24.5 × 15.5 cm. (paper-bound). 1949. His Majesty's Stationery Office, London. Price, 4 s. 0 d. net.
- Maternity in Great Britain: A Survey of Social and Economic Aspects of Pregnancy and Childbirth undertaken by a Joint Committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee.* 252 pages; 22.5 × 14.5 cm. 1949. Oxford University Press, New York. Price, \$4.00.
- Pathologie des Kohlehydratstoffwechsels.* By PROF. DR. E. FRANK, Direktor der II. medizinischen Klinik der Universität Istanbul. 342 pages; 22.5 × 15.5 cm. 1949. Benno Schwabe & Co., Verlag, Basel; Imported by Grune & Stratton, Inc., New York. Price, fr. 24.
- The Pharmacologic Principles of Medical Practice: A Textbook on Pharmacology and Therapeutics for Medical Students, Physicians, and the Members of the Professions Allied to Medicine.* By JOHN C. KRANTZ, JR., Professor of Pharmacology, School of Medicine, University of Maryland, etc.; and C. JELLEFF CARR, Associate Professor of Pharmacology, School of Medicine, University of Maryland. 980 pages; 23.5 × 16 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$10.00.
- The Physiology of the Eye.* By HUGH DAVSON, D.Sc. (Lond.), Honorary Research Associate, University College, London, etc.; with a Foreword by SIR STEWART DUKE-ELDER, K.C.V.O., M.A., D.Sc., Ph.D., M.D., F.R.C.S. 451 pages; 22.5 × 14 cm. 1949. The Blakiston Company, Philadelphia. Price, \$7.50.
- Psychodynamics and the Allergic Patient.* By HAROLD A. ABRAMSON, M.D., F.A.C.A., Associate Physician for Allergy, The Mount Sinai Hospital, New York, etc. Panel Discussion: RUDOLF L. BAER, M.D., ETHAN ALLAN BROWN, M.D., HAL M. DAVISON, M.D., R. O. SPURGEON ENGLISH, M.D., FRANK FREMONT-SMITH, M.D., J. A. P. MILLET, M.D., M. MURRAY PESHKIN, M.D., HOMER E. PRINCE, M.D., SANDOR RADO, M.D., and EDWARD WEISS, M.D. 81 pages; 20 × 13.5 cm. 1948. The Bruce Publishing Company, Saint Paul. An Official Publication of The American College of Allergists. Price, \$2.50.
- The Venereal Diseases: A Manual for Practitioners and Students.* 2nd Ed. By JAMES MARSHALL, M.D., B.S., M.R.C.S., L.R.C.P., Director, Venereal Diseases Clinic, Royal Northern Hospital, London, etc. 369 pages; 22 × 14 cm. 1949. Macmillan Company of London—Agents: Macmillan Company of New York. Price, \$5.50.

\* Incorporating the Third Edition of "Electrocardiograms" with 100 illustrations.

## COLLEGE NEWS NOTES

### AMERICAN COLLEGE OF PHYSICIANS DIRECTORY TO BE PUBLISHED IN AUTUMN OF 1949

Prepublication orders had exceeded 2,000 by early March, assuring publication of the 1949 Directory of the American College of Physicians. Membership Rosters only have been published since the last Directory in 1941 because of the many changes and restrictions imposed by World War II and by excessive cost of printing since then. The Rosters served an important but limited need, and a full Directory containing current professional information about its members as well as up-to-date information concerning the organization and activities of the College, is greatly needed.

A Directory Information Form will be mailed this Spring to each member of the College including those newly elected during the 1949 Annual Session. The information which it contains when returned to the College will be used in preparing the member's Directory entries. Members are urged to read carefully the instructions printed on this form as to character and extent of information to be published in the Directory, and manner of presentation. They are also requested to return the forms as promptly as possible, for the preparation of a complete and accurate Directory is necessarily time-consuming and publication in the Autumn of 1949 is the goal.

The cost of the 1949 Directory if ordered in advance of publication is \$4.00 to members of the American College of Physicians, and \$5.00 to non-members, institutions, firms, etc., to be billed to all at time of delivery. The cost after publication date has not yet been set. Members who have not yet reserved their copies are urged to do so at once, using the Prepublication Directory Order Forms mailed to them in January and in February.

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### A. C. P. POSTGRADUATE COURSES

At this time, six of the Postgraduate Courses offered by the College on the Spring 1949 Schedule have been concluded.

There are still accommodations available in Course No. 7, Cardiovascular Disease, Philadelphia Institutions, May 2-7, 1949, Dr. William G. Leaman, Jr., Director; and in Course No. 9, Endocrinology, Tufts College Medical School, Boston, June 13-18, 1949, Dr. Edwin B. Astwood, Director. Course No. 8, Physiological Basis for Internal Medicine, University of Pennsylvania Graduate School of Medicine, Philadelphia, May 9-14, 1949, Dr. Julius H. Comroe, Jr., Director, is already greatly over-subscribed.

For the information of members of the College and readers of the ANNALS OF INTERNAL MEDICINE, the detailed outlines of Courses No. 7 and No. 9 follow. All registrations are handled through the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

#### COURSE No. 7—CARDIOVASCULAR DISEASE

(May 2-7, 1949)

Philadelphia Institutions

The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., *Director*

(Minimal Registration, 50; Maximal Registration, 90)

Fees: A.C.P. Members, \$30.00. Non-members, \$60.00

*Consulting Committee*

Edward L. Bortz, M.D., F.A.C.P.  
 Charles L. Brown, M.D., F.A.C.P.  
 Thomas M. Durant, M.D., F.A.C.P.  
 William A. Jeffers, M.D.  
 Louis B. Laplace, M.D., F.A.C.P.  
 Thomas M. McMillan, M.D., F.A.C.P.  
 William D. Stroud, M.D., F.A.C.P.

*Officers of Instruction*

- Samuel Bellet, M.D., F.A.C.P., Assistant Professor of Cardiology, University of Pennsylvania Graduate School of Medicine; Clinical Assistant Professor of Medicine, Woman's Medical College of Pennsylvania; Associate Editor, American Heart Journal; Philadelphia, Pa.
- Charles L. Brown, M.D., F.A.C.P., Dean and Professor of Medicine. The Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa.
- Julius H. Comroe, Jr., M.D., F.A.C.P., Professor of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine; Clinical Physiologist, Hospital of the University of Pennsylvania; Philadelphia, Pa.
- André F. Cournand, M.D., Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.
- Arthur C. DeGraff, M.D., F.A.C.P., Samuel A. Brown Professor of Therapeutics and Chief of Cardiac Clinic, New York University College of Medicine; Visiting Physician, Bellevue Hospital, New York, N. Y.
- William Dock, M.D., F.A.C.P., Professor of Medicine, Long Island College of Medicine; Director of Medicine, Long Island Division, Kings County Hospital; Brooklyn, N. Y.
- Harry F. Dowling, M.D., F.A.C.P., Clinical Professor of Medicine, George Washington University School of Medicine; Chief, George Washington Medical Division, Gallinger Municipal Hospital; Washington, D. C.
- Robert D. Dripps, M.D., Associate Professor of Anesthesiology in Surgery, University of Pennsylvania School of Medicine and Graduate School of Medicine; Anesthesiologist, Hospital of the University of Pennsylvania, Philadelphia, Pa.
- Thomas M. Durant, M.D., F.A.C.P., Professor of Clinical Medicine, Temple University School of Medicine; Visiting Physician, Philadelphia General Hospital; Philadelphia, Pa.
- Joseph Edeiken, M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania School of Medicine; Cardiologist, Medical Service No. 1, Mount Sinai Hospital; Philadelphia, Pa.
- William E. Ehrich, M.D., Professor of Pathology and Chairman of the Department of Pathology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.
- Mortimer S. Falk, M.D., Assistant Instructor in Dermatology and Syphilology, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- William I. Geffer, M.D., Clinical Assistant Professor of Medicine, Woman's Medical College of Pennsylvania, Philadelphia, Pa.
- Emanuel Goldberger, M.D., Lecturer in Medicine, Columbia University College of Physicians and Surgeons; Adjunct Physician, Montefiore Hospital for Chronic Diseases; Cardiographer and Associate Physician, Lincoln Hospital; New York, N. Y.
- Burton E. Hamilton, M.D., F.A.C.P., Instructor in Medicine, Harvard Medical School (Courses for Graduates); Cardiologist, Boston Lying-In Hospital and New England Deaconess Hospital; Consultant in Cardiology, Palmer Memorial Hospital; Boston, Mass.

- John P. Hubbard, M.D., Assistant Professor of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Harold L. Israel, M.D., F.A.C.P., Assistant Professor of Medicine, Woman's Medical College of Pennsylvania; Assistant Visiting Physician, Philadelphia General Hospital; Philadelphia, Pa.
- Julian Johnson, M.D., F.A.C.S., Associate Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Louis N. Katz, M.D., F.A.C.P., Director of Cardiovascular Research, Michael Reese Hospital; Professorial Lecturer in Physiology, University of Chicago; Chicago, Ill.
- Seymour S. Kety, M.D., Professor of Clinical Physiology, University of Pennsylvania Graduate School of Medicine; Associate Clinical Physiologist, Hospital of the University of Pennsylvania; Philadelphia, Pa.
- Louis B. LaPlace, M.D., F.A.C.P., Associate in Medicine, Jefferson Medical College of Philadelphia, Philadelphia, Pa.
- William G. Leaman, Jr., M.D., F.A.C.P., Professor of Medicine and Chairman of the Department of Medicine, Woman's Medical College of Pennsylvania; Visiting Physician, Philadelphia General Hospital; President, Philadelphia Heart Association; Philadelphia, Pa.
- Leo Loewe, M.D., Assistant Professor of Clinical Medicine, Long Island College of Medicine; Attending Physician and Director of Thrombo-embolic Research Unit, Jewish Hospital; Brooklyn, N. Y.
- Alexander Margolies, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- H. M. Marvin, M.D., Associate Clinical Professor of Medicine, Yale University School of Medicine; Attending Physician, Grace-New Haven Community Hospital; President-Elect, American Heart Association; New Haven, Conn.
- Thomas M. McMillan, M.D., F.A.C.P., Professor of Clinical Medicine, School of Medicine, and Associate Professor of Cardiology, Graduate School of Medicine, University of Pennsylvania; Chief of Division of Cardiology, Philadelphia General Hospital; Editor-in-Chief, American Heart Journal; Philadelphia, Pa.
- Hugh Montgomery, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine; Physician-in-Charge, Peripheral Vascular Section, Hospital of the University of Pennsylvania; Philadelphia, Pa.
- Meyer Naide, M.D., Associate in Medicine, University of Pennsylvania School of Medicine; Physician-in-Charge, Peripheral Vascular Clinic, Mount Sinai Hospital; Philadelphia, Pa.
- Herman W. Ostrum, M.D., Assistant Professor Radiology, University of Pennsylvania Graduate School of Medicine; Roentgenologist, Philadelphia General Hospital, Philadelphia, Pa.
- George A. Perera, M.D., Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.
- I. S. Ravdin, M.D., F.A.C.S., John Rhea Barton Professor of Surgery and Director of the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine; Professor of Surgery, University of Pennsylvania Graduate School of Medicine; Philadelphia, Pa.
- Hobart A. Reimann, M.D., F.A.C.P., McGee Professor of the Principles and Practice of Medicine, Jefferson Medical College of Philadelphia, Philadelphia, Pa.
- George P. Robb, M.D., F.A.C.P., Consultant in Cardiology, Cardiovascular Research Unit, Veterans Administration; Consultant in Cardiology to the Surgeon General, U. S. Army; Assistant Medical Director, Metropolitan Life Insurance Co., New York, N. Y.

- Howard A. Rusk, M.D., F.A.C.P., Professor and Chairman of the Department of Rehabilitation and Physical Medicine, New York University College of Medicine; Chief of Rehabilitation Service, Bellevue Hospital; Director, New York University-Bellevue Medical Center Institute of Rehabilitation and Physical Medicine; New York, N. Y.
- Lauren H. Smith, M.D., F.A.C.P., Professor of Psychiatry and Chairman of the Department of Psychiatry, University of Pennsylvania Graduate School of Medicine; Administrator and Physician-in-Chief, Institute of the Pennsylvania Hospital; Philadelphia, Pa.
- Reginald H. Smithwick, M.D., F.A.C.S., Professor of Surgery, Boston University School of Medicine, Surgeon-in-Chief, Massachusetts Memorial Hospitals; Boston, Mass.
- Isaac Starr, M.D., Milton Bixler Hartzell Research Professor of Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Eugene A. Stead, Jr., M.D., F.A.C.P., Professor of Medicine, Duke University School of Medicine; Physician-in-Chief, Duke Hospital; Durham, N. C.
- William D. Stroud, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.
- Helen B. Taussig, M.D., Associate Professor of Pediatrics, Johns Hopkins University School of Medicine; Director Children's Cardiac Clinic at the Harriet Lane Home of the Johns Hopkins Hospital; Baltimore, Md.
- Harry E. Ungerleider, M.D., F.A.C.P., Medical Director, Research, The Equitable Life Assurance Society of the United States, New York, N. Y.
- S. O. Waife, M.D., Instructor in Medicine, Woman's Medical College of Pennsylvania; Assistant Director in Charge of Medical Education, Philadelphia General Hospital; Philadelphia, Pa.
- Paul D. White, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital; Consultant in Cardiovascular Disease, National Heart Institute, Bethesda; Boston, Mass.
- John H. Willard, M.D., F.A.C.P., Associate Professor of Medicine, Woman's Medical College of Pennsylvania; Assistant Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine; Philadelphia, Pa.
- Charles C. Wolferth, M.D., F.A.C.P., Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Francis C. Wood, M.D., F.A.C.P., Professor of Medicine and Chairman of the Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- Wallace M. Yater, M.D., F.A.C.P., Director of the Yater Clinic; Formerly Professor of Medicine, Georgetown University School of Medicine; Washington, D. C.

This course will place emphasis on recent advances, including current knowledge, diagnosis, and treatment. Some attention will be given to such subjects as electrocardiography, radiology, catheterization of the heart, and the surgical treatment of special cardiac conditions. The course will include lectures, panel discussions, and, on two afternoons, suitable clinical demonstrations.

The lectures will be given in the new Auditorium of the American College of Physicians' Building, 4200 Pine St., Philadelphia, and the clinical work, Wednesday afternoon and Friday afternoon, will be given in the Surgical Amphitheatre of the Philadelphia General Hospital, 34th St. and Curie Ave., Philadelphia, Pa.

Courtesy of the Library of the College of Physicians of Philadelphia will be extended to registrants of the course. A reception and buffet supper will be given for members of the class and their wives or relatives at the College Headquarters on the first evening, May 2. Other social events will be arranged, participation to be optional.

*Outline of Course**Monday, May 2.*

A.M. Session.

- 9:00- 9:15    Introductory Remarks and Announcements.  
                  Dr. Leaman.
- 9:15-10:00    Psychiatric Treatment in Cardiovascular Conditions.  
                  Dr. Smith.
- 10:00-10:45    Clinical Features of the Commoner Types of Congenital Cardiac Defects.  
                  Dr. Taussig.
- 10:45-11:00    Intermission.
- 11:00-11:45    Cardiac Catheterization in the Diagnosis of Congenital Cardiac Defects.  
                  Dr. Cournand.
- 11:45-12:30    Surgical Treatment of Congenital Cardiac Defects.  
                  Dr. Johnson.

P.M. Session.

- 2:00- 2:50    Clinical Features of the Commoner Types of Congenital Cardiac Defects (concluded).  
                  Dr. Taussig.
- 2:50- 3:45    Angiocardiography.  
                  Dr. Robb.
- 3:45- 4:00    Intermission.
- 4:00- 5:00    Cardiac Enlargement.  
                  Dr. Ungerleider.
- 5:30            RECEPTION AND BUFFET SUPPER for Members of the Course  
                  and their Wives at the College Headquarters, 4200 Pine Street.

*Tuesday, May 3.*

A.M. Session.

- 9:00- 9:50    Pathogenesis of Rheumatic Fever.  
                  Dr. Ehrich.
- 9:50-10:45    Clinical Aspects of Rheumatic Heart Disease.  
                  Dr. LaPlace.
- 10:45-11:00    Intermission.
- 11:00-11:45    Comments on the Treatment of Rheumatic Fever.  
                  Dr. Hubbard.
- 11:45-12:30    Question and Answer Period. Rheumatic Fever and Rheumatic Heart Disease.  
                  Drs. Ehrich, LaPlace, Hubbard, Margolies and Leaman.

P.M. Session.

- 2:00- 2:50    Some Observations on Penicillin Treatment in Cardiovascular Syphilis.  
                  Drs. Edeiken and Falk.
- 2:50- 3:45    Subacute Bacterial Endocarditis: Diagnosis and Present Day Treatment.  
                  Dr. Loewe.
- 3:45- 4:00    Intermission.
- 4:00- 5:30    Acute Myocarditis. A Panel Discussion.  
                  Drs. Loewe, Geffer, Dowling, Reimann and Leaman.

*Wednesday, May 4.*

## A.M. Session.

- 9:00- 9:50 The Treatment of the Cardiac Arrhythmias.  
Dr. Bellet.
- 9:50-10:30 Anti-Coagulant Therapy.  
Dr. Yater.
- 10:30-10:45 Pulmonary Arteriovenous Fistula.  
Dr. Yater.
- 10:45-11:00 Intermission.
- 11:00-11:50 Recent Advances in the Treatment of Peripheral Vascular Disorders.  
Dr. Naide.
- 11:50-12:30 Thrombosis and Embolism. A Panel Discussion.  
Drs. Yater, Montgomery, Naide, Ravdin and Leaman.

## P.M. Session.

Surgical Amphitheatre, Philadelphia General Hospital  
34th Street and Curie Avenue

- 2:00-2:30 Management of Acute Myocardial Infarction in the Diabetic Patient.  
Dr. Waife.
- 2:30- 3:00 The Physiology and Pharmacology of the Coronary Circulation.  
Dr. Kety.
- 3:00- 3:15 Intermission.
- 3:15- 4:45 Recent Advances in Electrocardiography.  
Dr. Katz.
- 4:45- 5:30 Some Facts Concerning Cholesterol Metabolism and Their Clinical Application.  
Dr. Katz.
- 5:30-6:00 Government Aids in Cardiovascular Research.  
Dr. White.

*Thursday, May 5.*

## A.M. Session.

- 9:00-10:15 Pericarditis. Diagnosis and Management.  
Drs. McMillan, Bellet and Ostrum.
- 10:15-10:45 The Effect of Nicotine on the Cardiovascular System.  
Dr. Comroe.
- 10:45-11:00 Intermission.
- 11:00-11:50 Unipolar Leads.  
Dr. Goldberger.
- 11:50-12:30 Question and Answer Period. Electrocardiography.  
Drs. Bellet, Goldberger, McMillan, Wood and Wolferth.

## P.M. Session.

- 2:00- 2:50 Diet and Rest in Congestive Cardiac Failure.  
Dr. Dock.
- 2:50- 3:50 Modern Aspects of Digitalis Therapy.  
Dr. DeGraff.
- 3:50- 4:00 Intermission.
- 4:00- 4:40 Oxygen Therapy.  
Dr. Comroe.
- 4:40- 5:30 Mercurial Diuretics.  
Dr. Durant.

*Evening Session*

- 8:30 This meeting will be held at the College of Physicians of Philadelphia, 19 S. 22nd Street (Mitchell Hall, 2nd floor). It will be a joint meeting with the Philadelphia Heart Association and Section on General Medicine, College of Physicians of Philadelphia.

## THE MECHANISM OF CONGESTIVE HEART FAILURE

EUGENE A. STEAD, JR., M.D., F.A.C.P.

Discussers: Drs. Starr and Stroud.

*Friday, May 6.*

## A.M. Session.

- 9:00- 9:50 The Evaluation of the Cardiac Patient as a Surgical Risk.  
Dr. Wood.
- 9:50-10:45 The Heart in Pregnancy.  
Dr. Hamilton.
- 10:45-11:00 Intermission.
- 11:00-12:00 The Problem of Anesthesia in the Presence of Heart Disease.  
Dr. Dripps.
- 12:00-12:30 The Heart in Surgery. A Panel Discussion.  
Drs. Dripps, Wood, Johnson, Hamilton and Leaman.

## P.M. Session.

Surgical Amphitheatre, Philadelphia General Hospital  
34th Street and Curie Avenue

- 2:00- 3:00 The Medical Treatment of Coronary Heart Disease.  
Dr. Marvin.
- 3:00- 3:45 The Medical Treatment of Hypertensive Cardiovascular Disease.  
Dr. Perera.
- 3:45- 4:00 Intermission.
- 4:00- 5:00 The Surgical Treatment of Hypertension.  
Dr. Smithwick.
- 5:00- 5:45 Question and Answer Period.  
Drs. Marvin, Perera, Brown, Smithwick, Stroud and Leaman.

*Saturday, May 7.*

## A.M. Session.

- 9:00- 9:30 Pulmonary Heart Disease.  
Dr. Israel.
- 9:30-10:00 Cardiac Symptoms Secondary to Gastrointestinal Tract Disturbances.  
Dr. Willard.
- 10:00-11:00 Some Problems in the Rehabilitation of the Cardiac Patient.  
Dr. Rusk.
- 11:00-11:15 Intermission.
- 11:15-12:30 Review of Clinical Electrocardiography (Case Studies from the Heart Station, Philadelphia General Hospital).  
Drs. Bellet and McMillan.



## COURSE No. 9—ENDOCRINOLOGY

(June 13-18, 1949)

Tufts College Medical School (Postgraduate Division), Boston, Mass.

*Director*

EDWIN B. ASTWOOD, M.D., F.A.C.P.

*Associate Directors*

E. W. DEMPSEY, Ph.D.

ROY O. GREEP, Ph.D.

(Minimal Registration, 40; Maximal Registration, 100)

Fees: A.C.P. Members, \$30.00. Non-members, \$60.00

*Officers of Instruction*

Fuller Albright, M.D., Associate Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital.

E. B. Astwood, M.D., Ph.D., F.A.C.P., Research Professor of Medicine, Tufts College Medical School; Endocrinologist, Joseph H. Pratt Diagnostic Hospital.

Joseph C. Aub, M.D., Professor of Research Medicine and Director of the Medical Laboratories of the Collis P. Huntington Memorial Hospital, Harvard Medical School; Physician, Massachusetts General Hospital.

F. C. Bartter, M.D., Research Fellow in Medicine, Harvard Medical School; Clinical and Research Fellow in Medicine, Massachusetts General Hospital.

J. S. L. Browne, M.D., C.M., Ph.D., F.R.S.C., F.A.C.P., Professor of Medicine, McGill University Faculty of Medicine; Director, University Clinic, Royal Victoria Hospital; Montreal, Que., Can.

Earle M. Chapman, M.D., F.A.C.P., Instructor in Medicine, Harvard Medical School; Associate Physician, Massachusetts General Hospital.

George W. Crile, Jr., M.D., F.A.C.S., Member, Surgical Staff, Cleveland Clinic Foundation, Cleveland, Ohio.

M. Edward Davis, M.D., F.A.C.S., Joseph Bolivar DeLee Professor of Obstetrics and Gynecology, University of Chicago; Obstetrician and Gynecologist, Chicago Lying-In Hospital, Chicago, Ill.

Edward W. Dempsey, Ph.D., Associate Professor of Anatomy, Harvard Medical School.

Konrad Dobriner, M.D., Member, Sloan-Kettering Institute for Cancer Research, New York, N. Y.

Kendall Emerson, Jr., M.D., Associate in Medicine, Harvard Medical School; Senior Associate in Medicine, Peter Bent Brigham Hospital.

Earl T. Engle, Ph.D., Professor of Anatomy, Columbia University College of Physicians and Surgeons, New York, N. Y.

John W. Everett, Ph.D., Associate Professor of Anatomy, Duke University School of Medicine, Durham, N. C.

Louis F. Fieser, Ph.D., Sheldon Emery Professor of Organic Chemistry, Harvard University, Cambridge, Mass.

Robert Gaunt, Ph.D., Professor of Zoology, Syracuse University, Syracuse, N. Y.

Roy O. Grep, Ph.D., Associate Professor of Dental Science, Harvard School of Dental Medicine.

Carl G. Hartman, Ph.D., Director, Division of Physiology, Ortho Research Foundation, Raritan, N. J.

- Roy Hertz, M.D., Ph.D., Assistant Clinical Professor of Medicine, The George Washington University School of Medicine; Chairman, Endocrinology Section, National Cancer Institute; Washington, D. C.
- Frederick L. Hisaw, Ph.D., Professor of Zoology, Harvard University, Cambridge, Mass.
- Roy G. Hoskins, M.D., Ph.D., Consultant in Medical Sciences, Boston Branch Office of Naval Research.
- John Eager Howard, M.D., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.
- Dwight J. Ingle, Ph.D., Senior Research Scientist (Physiology), Research Laboratories, The Upjohn Company, Kalamazoo, Mich.
- F. D. W. Lukens, M.D., Associate Professor of Medicine and Director of the George S. Cox Medical Research Institute, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- E. Perry McCullagh, M.D., F.A.C.P., Director, Section on Endocrinology and Metabolism, Cleveland Clinic Foundation, Cleveland, Ohio.
- Gregory Pincus, Sc.D., Director of Laboratories, Worcester Foundation for Experimental Biology; Research Professor of Physiology, Tufts College Medical School; Shrewsbury, Mass.
- John Rock, M.D., Clinical Professor of Gynecology, Harvard Medical School; Visiting Surgeon, Free Hospital for Women; Consulting Obstetrician, Massachusetts General Hospital.
- Jane A. Russell, Ph.D., Instructor in Physiological Chemistry, Yale University School of Medicine, New Haven, Conn.
- George Sayers, Ph.D., Associate Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah.
- Hans Selye, M.D., Ph.D., D.Sc., Professor of Experimental Medicine and Surgery, and Director of the Institute of Experimental Medicine and Surgery, University of Montreal Faculty of Medicine, Montreal, Que., Can.
- Malcolm M. Stanley, M.D., Instructor in Medicine, Tufts College Medical School; Research Associate in Medicine, Joseph H. Pratt Diagnostic Hospital.
- Somers H. Sturgis, M.D., Clinical Associate in Gynecology, Harvard Medical School; Assistant Surgeon, Massachusetts General Hospital; Chief, Vincent Memorial Hospital Research Laboratory.
- S. J. Thannhauser, M.D., Ph.D., Professor of Clinical Medicine, Tufts College Medical School; Associate Physician-in-Chief, Joseph H. Pratt Diagnostic Hospital.
- W. P. VanderLaan, M.D., Assistant Professor of Medicine, Tufts College Medical School; Assistant Physician, Joseph H. Pratt Diagnostic Hospital.
- H. B. Van Dyke, M.D., Ph.D., Hosack Professor of Pharmacology, Columbia University College of Physicians and Surgeons, New York, N. Y.
- A. E. Wilhelmi, Ph.D., Assistant Professor of Physiological Chemistry, Yale University School of Medicine, New Haven, Conn.

This course is designed for internists who are especially interested in endocrinology and who desire further training in the basic physiology and biochemistry of the subject.

A Presiding Chairman has been assigned to each session to guide the discussion, and various faculty members will be present to provide an opportunity for free discussion among the faculty and the students.

The course will be held in the *New England Medical Center* (Joseph H. Pratt Diagnostic Hospital, Ziskind Research Laboratories, Boston Floating Hospital, Boston Dispensary, and the New England Center Hospital).

*Outline of Course**Monday, June 13.*

A.M. Session. DR. ROY G. HOSKINS, Chairman.

9:00- 9:15 Registration.

9:15- 9:30 Introduction.

Dr. Hoskins.

9:30-10:15 Histochemistry of the Endocrine Glands.

Dr. Dempsey.

10:30-11:15 Integrative Functions of the Endocrine System.

Dr. Greep.

11:30-12:15 Experimental and Clinical Aspects of Nutrition and Endocrine Function.

Dr. Hertz.

P.M. Session. DR. S. J. THANNHAUSER, Chairman.

2:00- 2:45 Parathyroids and Mineral Metabolism.

Dr. Greep.

3:00- 3:45 Tetany and Hyperparathyroidism.

Dr. Bartter.

4:00- 5:00 Metabolic Bone Disease and Hyperadrenocorticism.

Dr. Albright.

*Tuesday, June 14.*

A.M. Session. DR. GREGORY PINCUS, Chairman.

9:00- 9:45 Hormonal and Neural Factors Regulating the Chronology of the Mam-  
malian Reproductive Cycle.

Dr. Everett.

10:00-10:45 Endocrine Control of Menstrual Cycle.

Dr. Hisaw.

11:00-12:00 The Physiological Significance of the Common Menstrual Irregu-  
larities.

Dr. Davis.

P.M. Session. DR. JOHN ROCK, Chairman.

2:15- 2:45 Clinical Investigation of Sterility in Women.

Dr. Sturgis.

3:00- 4:00 The Testis Biopsy in Infertility.

Dr. Engle.

4:15- 5:15 Hypogonadism and Sterility in the Male.

Dr. McCullagh.

*Wednesday, June 15.*

A.M. Session. DR. EARL T. ENGLE, Chairman.

9:00- 9:45 Migration and Maturation of Sperm in the Male Genital Tract.

Dr. Hartman.

10:00-10:45 Transport and Survival of Sperm in the Female Genital Tract.

Dr. Hartman.

11:00-12:00 The Physiological Significance of the Posterior Pituitary Gland.

Dr. Van Dyke.

P.M. Session. DR. H. B. VAN DYKE, Chairman.

2:00- 2:45 Adrenal Cortex in Salt-and-Water Metabolism.

Dr. Gaunt.

- 3:00- 3:45 Regulation of the Secretory Activity of the Adrenal Cortex.  
Dr. Sayers.  
4:00- 4:45 The Relationship of the Adrenal Cortex to Organic Metabolism.  
Dr. Ingle.

*Thursday, June 16.*

A.M. Session. DR. J. S. L. BROWNE, Chairman.

- 9:00- 9:45 Addison's Disease.  
Dr. Emerson.  
10:00-11:00 Preparation and Actions of Anterior Pituitary Growth Hormone.  
Dr. Wilhelmi.  
11:15-12:15 Metabolic Effects of the Anterior Pituitary.  
Dr. Russell.

P.M. Session. DR. GREGORY PINCUS, Chairman.

- 2:00- 2:45 Factors Regulating Adrenal Cortical Activity Under Normal and Pathological Conditions.  
Dr. Selye.  
3:00- 4:00 Chemistry of the Steroid Hormones.  
Dr. Fieser.  
4:15- 5:15 Steroid Hormone Metabolism.  
Dr. Dobriner.

#### THURSDAY EVENING—Dinner

*Friday, June 17.*

A.M. Session. DR. GEORGE W. CRILE, JR., Chairman.

- 9:00- 9:45 Physiology of the Thyroid Gland.  
Dr. Astwood.  
10:00-10:45 Diagnosis of Thyroid Disorders.  
Dr. Howard.  
11:00-11:30 Evaluation of Human Thyroid Function with I <sup>131</sup>.  
Dr. Stanley.  
11:45-12:15 Antithyroid Compounds in Hyperthyroidism.  
Dr. VanderLaan.

P.M. Session. DR. JOHN EAGER HOWARD, Chairman.

- 2:00- 2:45 Use of Radioactive Iodine in the Therapy of Hyperthyroidism and Thyroid Tumors.  
Dr. Chapman.  
3:00- 4:00 Indications for Surgical Treatment of Thyroid Diseases.  
Dr. Crile.  
4:15- 5:00 General Discussion of Therapy in Thyroid Diseases.  
Dr. Howard, Moderator.

*Saturday, June 18.*

A.M. Session. DR. JOSEPH C. AUB, Chairman.

- 9:00-10:00 The Pathogenesis of Diabetes.  
Dr. Lukens.  
10:15-11:00 Structure and Endocrine Function of the Placenta.  
Dr. Dempsey.  
11:15-12:15 Endocrine Physiopathology of Pregnancy.  
Dr. Browne.

A REPORT ON POSTGRADUATE COURSE NO. 3, CLINICAL MEDICINE FROM THE  
HEMATOLOGIC VIEWPOINT

The American College of Physicians had upon its Spring, 1949, schedule, February 14-19, a course entitled "Clinical Medicine from the Hematologic Viewpoint," organized and directed by Dr. Charles A. Doan, F.A.C.P., Dean and Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio. In addition to faculty members from the Ohio State University, Dr. Marion F. Beard, F.A.C.P., University of Louisville School of Medicine, Louisville; Dr. Theodore S. Evans, F.A.C.P., Yale University School of Medicine, New Haven; Dr. Malcolm Hargraves of the Mayo Clinic, Rochester; Dr. Henry E. Wilson, Jr., of Northwestern University Medical School, Chicago; Dr. Sloan J. Wilson of the University of Kansas School of Medicine, Kansas City; and Dr. Ernest von Lauda, Professor of Medicine at the University of Vienna, Vienna, Austria, constituted a Visiting Faculty.

One day each was devoted to the following general themes: the histo- and pathologic-physiology of the blood and blood-cell forming organs as the basis for a better understanding of human disease; the anemic states; the white blood cell dyscrasias; disease syndromes involving the spleen, liver and bone marrow; the hemorrhagic syndromes; miscellaneous topics. Forty-five physicians coming from various parts of the United States and Canada were registered in the course. Each afternoon they were divided into four groups for ward rounds, round table conferences and laboratory work with both supravital and fixed preparations. Those who were interested in the Regional American Red Cross Blood Center were taken for a personal inspection and tour of the Center one evening. A shipment of radio-active phosphorus from Oak Ridge was received during the week, and a group of interested persons from the class visited the laboratory where this was prepared for clinical therapeutic use. On another day, a special feature was the arrangement for a splenectomy with the fresh material carried directly to the laboratory for afternoon work; and a number of the men went to the operating room and observed the surgery. On one evening, the Department of Physics, with the Chairman of the Department as host, took thirty-five of the group to see the cyclotron and the demonstration of the physical apparatus with biological application such as the electron microscope, the Vandergraf generator and other apparatus significant in biological research. Even after the course was formally concluded at noon on Saturday, a number of the men remained in the afternoon for additional study of the fixed slides and the graphs and demonstrations which were prepared for them.

The course gave a considerable latitude in election for the men in a variety of experiences, and those who desired full-time with the microscopes were permitted to do so, while the clinicians who wanted more clinical outlets, were given the ward round opportunity.

Many niceties were introduced such as mid-morning and mid-afternoon recesses, the serving of coffee and tea and cookies, and an evening cocktail party and dinner the first day, at which Dr. Ernest von Lauda, Professor of Medicine at the University of Vienna, gave a talk on "The Present Status of Medicine in Europe." Members of the College who were registered in the course have expressed great appreciation of this excellent course.

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ACP REGIONAL MEETING IN OMAHA

The Annual Regional Meeting of the College for the State of Nebraska was held at Omaha on February 19, 1949, under the direction of Dr. Joseph D. McCarthy, Governor for that state. Out of 66 members in the state, 52 were in attendance, 3

members came from Iowa, and there were 6 guests, making a total of 61. The attendance would have been greater except for hazardous road conditions resulting from sleet storms about the state.

A very excellent scientific program was rendered, under the Chairmanship of Dr. Adolph Sachs, F.A.C.P., a former Governor of that state. Dr. Walter L. Palmer, F.A.C.P., Chicago, Chairman of the Board of Governors of the American College of Physicians, was the chief guest speaker. He presented a paper entitled, "The Treatment of Intractable Peptic Ulcer," on the scientific program, and he addressed the dinner meeting in the evening on "Problems Confronting the American College of Physicians and the American Board of Internal Medicine."

The next Annual Regional Meeting for Nebraska will be held in Lincoln during February or March, 1950.

#### WESTERN MICHIGAN HELD ACP REGIONAL MEETING

Members of the American College of Physicians located in Western Michigan held a Regional Meeting at the Kent Country Club, Grand Rapids, Mich., February 23, 1949, under the Chairmanship of Dr. Gordon W. Balyeat, F.A.C.P.; 70 members of the College and guests were present.

The program consisted of the following: "The Use of Drugs in Vascular Disease," Noyes L. Avery, Jr., M.D., F.A.C.P.; "Laboratory Problems in the Serodiagnosis of Certain Mycotic Infections," Paul A. Van Pernis, M.D. (by invitation); "Albright's Syndrome," Gordon W. Balyeat, M.D., F.A.C.P.; "An Unusual Bone Disease," Carl B. Beeman, M.D., F.A.C.P. There were exhibits through the courtesy of C. Allen Payne, M.D., and others, and in the evening Dr. Burton R. Corbin, F.A.C.P., was toastmaster at a dinner at which Dr. Merrill Wells, F.A.C.P., gave an address of welcome, and Dr. Clarence W. Muehlberger, Chief Toxicologist at the Michigan State Department of Health Laboratories, gave an address, "Scientific Methods of Criminal Investigation."

#### UTAH-IDAHO REGIONAL MEETING

The 1949 meeting of members of the College in Utah and Idaho was held at the Salt Lake General Hospital, Salt Lake City, Utah, on March 4, 1949, through the collaboration of Louis E. Viko, M.D., F.A.C.P., Salt Lake City, Governor for Utah, Samuel M. Poindexter, M.D., F.A.C.P., Boise, Governor for Idaho, and Maxwell W. Wintrobe, M.D., F.A.C.P., Salt Lake City, Chairman of the Program Committee. First Vice President William S. Middleton, M.D., F.A.C.P., Madison, Wis., was the guest of honor; he conducted a clinical pathological conference and spoke at the dinner meeting on "Therapia Magna Sterilisans." A feature of the meeting was the round table discussion conducted at the luncheon by G. Gill Richards, M.D., F.A.C.P., Salt Lake City.

The following cases and papers were presented at the morning and afternoon sessions: J. C. Nunemaker, Spondylitis in Identical Twins Raised Apart; R. H. Tyler, Clinical Manifestations and Inheritance of Encapsulothoracic Progressive Muscular Dystrophy; H. Brown, Potassium Metabolism in Diabetic Acidosis; H. H. Hecht, The Natural History of Coronary Artery Disease; R. D. Beech (Associate), An Unusual Case of Arterial Disease; Horace W. Davenport, Relationship of Electrolytes to Convulsive Seizures; Louis G. Moench, F.A.C.P., Some Somatic Aspects of Psychosomatic Medicine; G. R. Leymaster, Influenza Vaccines; B. V. Jager, Alterations of Serum Proteins in Disease; G. E. Cartwright, The Newer Knowledge of Pernicious Anemia;

J. F. Waldo, The Newer Antibiotics; P. F. Miner, Management of Bleeding Duodenal Ulcer; M. M. Wintrobe, F.A.C.P., Chemotherapy of Leukemia and Diseases Involving Lymph Nodes; Theodore C. Bauerlein, F.A.C.P., Gastroscopic Diagnosis of Stomach Lesions.

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#### ADDITIONAL LIFE MEMBERS

The American College of Physicians takes pride in announcing that, by their recent subscriptions, the following Fellows have been added to the Roster of Life Members of the College:

J. Russel Brink, Grand Rapids, Mich.  
Joseph E. J. Harris, Albuquerque, N. M.  
George R. Lacy, Pittsburgh, Pa.  
Harold W. Lovell, New York, N. Y.  
Harold C. Lueth, Omaha, Nebr.  
Carl L. Mauser, Oakland, Calif.  
Lester Neuman, Washington, D. C.  
John M. Rumsey, San Diego, Calif.  
Ben Shenson, San Francisco, Calif.

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#### MEETINGS OF OTHER SOCIETIES

The American Association of Railway Surgeons will hold its 61st Annual Meeting at the Drake Hotel, Chicago, Ill., on July 1 and 2, 1949.

The 15th Annual Meeting of the American College of Chest Physicians will be held at the Ambassador Hotel, Atlantic City, N. J., June 2 to 5, 1949.

The International Congress on Rheumatic Disease will be held at the Waldorf-Astoria Hotel, New York, N. Y., May 30 to June 3, 1949. More than 150 physicians from foreign countries are expected to attend. The meeting will contain morning plenary sessions and afternoon hospital clinics. The meeting is open; registration fee, \$10.00.

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#### POSTGRADUATE COURSE IN SAN FRANCISCO

A postgraduate course of 12 weeks' length in Psychiatry and Neurology will be offered at the University of California Medical School (the Langley Porter Clinic), in San Francisco, August 29–November 18, 1949. The course will be full-time; and will be conducted by Karl M. Bowman, M.D., Professor of Psychiatry, Chairman. Tuition, \$200.00. For course outline, communicate with Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, Calif.

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#### APPLICATIONS FOR RESEARCH FELLOWSHIPS IN SPINAL CORD DISEASE AND TRAUMA

Applications will be received to June 1, 1949, for a limited number of fellowships to facilitate investigation of spinal cord disease and trauma and the complications commonly associated with such disease and injury, by The National Paraplegia Foun-

dation. The Fellowships will be awarded by the Medical Advisory Committee, for the academic year 1949-50, and will carry a minimum stipend of \$3,000.00 a year. Candidates must demonstrate a capacity for medical research and must outline a program of meritorious study. Application forms may be secured from L. W. Freeman, M.D., Chairman, Medical Advisory Committee, National Paraplegia Foundation, Room 457, Hotel La Salle, Chicago 2, Ill.

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#### THE UNIVERSITY OF VIENNA AGAIN OFFERS POSTGRADUATE COURSES

The University of Vienna has recently announced that its clinical facilities for postgraduate study of medicine and surgery are available to doctors from overseas, that accommodations are well organized and are being handled exclusively in Vienna by the Oesterreichische Verkehrsbureau, which coöperates with all travel agents. The Austrian State Tourist Department, 48 East 48th Street, New York 17, N. Y., is the North American representative.

Courses are available in General Pathology, Pathological Histology, Surgery, X-Ray Diagnosis, Clinical Differential Diagnosis, Hematology, Internal Diseases, Electrocardiography, Clinical Endoscopy, Obstetrics, Gynecology, Psychiatry, Neurology, Dermatology, Microscopy, Otology, Laryngology, and in many other fields.

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Dr. J. Murray Kinsman, F.A.C.P., College Governor for the State of Kentucky, has been elected Dean of the University of Louisville School of Medicine, to assume office on July 1, 1949. Dr. John Walker Moore, present Dean, is resigning as of July 1, to return to private practice.



## OBITUARIES

## DR. LLEWELLYN R. COLE

Llewellyn Rathbun Cole, M.D., F.A.C.P., of Madison, Wis., died suddenly of a massive subarachnoid hemorrhage on December 31, 1948, at the age of 46.

Dr. Cole was born in Clintonville, Wis., December 17, 1902. He received his B.A. in 1926, and his doctorate in medicine in 1929, from the University of Wisconsin. After serving as resident physician in the Graduate Hospital, Philadelphia, from 1929 to 1931, he returned to the University of Wisconsin as an assistant physician in the Department of Student Health. In 1936, he became Assistant Professor of Clinical Medicine in the University of Wisconsin Medical School, and Director of Student Health. He was advanced to Professor of Clinical Medicine in 1938.

Dr. Cole retired in 1945 because of ill health, but returned to the University the following year as Co-ordinator of Graduate Medical Education, a position created to meet the increasing demands of the Medical School to extend medical education beyond the Campus. This opportunity enabled him to develop his previously recognized talents as a radio lecturer and a writer of script to bring the advances of science and health to radio listeners. In the following two and one half years of his life, he broadcast his radio program on the University station WHA. So successful was he that the officers of the State Medical Society invited him to take over their radio program, The March of Medicine, broadcast over 26 stations in the State.

Dr. Cole initiated a program to improve medical education and practice through a system of postgraduate medical short courses for general practitioners and refresher courses for specialists. He became a consultant on medical affairs to the President of the University and served on many University and Faculty committees. He was one of the planners of the "Wisconsin Center," a building to be used for the housing and instruction of groups coming to the University for short courses. To further medical education for the profession, Dr. Cole was organizing lectures to be broadcast over FM stations, as an experiment. In short, he took advantage of every means available for disseminating medical information to the profession and citizenry.

As a student Dr. Cole was elected to Alpha Omega Alpha. He held membership in the Dane County and State of Wisconsin Medical Societies, and was a Fellow of the American Medical Association. Elected a Fellow of the American College of Physicians in 1941, he gave valuable assistance to its regional and postgraduate programs. He was a senior staff member of the State of Wisconsin General Hospital.

With the death of Dr. Cole, we have lost a pioneer in health education, a gifted lecturer and writer, a counselor and coördinator of medical education, and an organizer and planner of medical courses.

KARVER L. PUESTOW, M.D., F.A.C.P.,  
Governor for Wisconsin

## DR. THOMAS BALFOUR DUNN

Dr. Thomas Balfour Dunn of Oakland, Calif., died suddenly at Fresno, on December 28, 1948. He was en route to Los Angeles to attend the Rose Bowl football game.

Dr. Dunn was born in Ventura, Calif., May 5, 1886. He received a B.S. degree in 1913, and his M.D. degree in 1916, both from the University of California. While still a senior medical student, he served an internship at the University of California Hospital. After graduation he received an honor internship in this hospital, serving from 1916 to 1917. During the years 1917 to 1920 he served in the U. S. Navy during World War I, being assigned to Asiatic duty. In 1920 Dr. Dunn entered medical practice at Shanghai, China, where he rapidly achieved prominence as an internist, enjoying a long and interesting career as chief of a diagnostic center. Many

important Chinese officials were patients of Dr. Dunn during his career in China, including Chiang Kai Shek and T. V. Soong. Dr. Dunn was a member of the Board of Governors of the County Hospital and the Shanghai General Hospital; served as President of the Shanghai Medical Society and the Foreign Practitioners' Medical Society. He was a Fellow of the London and Royal Societies of Tropical Medicine, and a member of the Chinese Medical Society.

During World War II he was imprisoned by the Japanese, losing all of his medical library, reprints and papers. In 1943 Dr. Dunn was returned to New York on the *Gripsholm* and was repatriated. He returned to California in 1944 and took up residence in Oakland, where he shortly became well established as a consultant in internal medicine. His appointments included the Staffs of the Samuel Merritt, Peralta, and Providence Hospitals, Oakland, and the Alta Bates Hospital in Berkeley. One of his first appointments after returning to California was as Lecturer in Tropical Medicine at the University of California Medical School, where considerable time was spent in establishing a clinic in Tropical Medicine and organizing the teaching of this subject.

Dr. Dunn was a diplomate of the Board of Internal Medicine and became a Fellow of the American College of Physicians in 1946. He was a member of the Alameda County and California State Medical Societies; a Fellow of the American Medical Association, the California Academy of Medicine and the American Society of Tropical Medicine.

Dr. Dunn possessed a distinguished bearing, a kindly, genial personality and a fund of common sense that attracted patients, and established contacts with his fellow practitioners. These factors led to a position of influence in his community during the too few years of life, after returning to his native California.

ERNEST H. FALCONER, M.D., F.A.C.P.

#### DR. LUIS ORTEGA

Dr. Luis Ortega of Havana, Cuba, died of cerebral hemorrhage on December 10, 1948, at the age of 76 years. He is survived by his wife, Mrs. Esperanza Ortega, a son, Dr. Luis Ortega, Jr., and six grandchildren.

Dr. Ortega graduated from the University of Havana in 1896. His high ranking led to his selection as intern, chief intern, and anesthesiologist in the "Nuestra Senora de las Mercedes" Hospital, now directed by his son, who is Assistant Professor of Clinical Medicine in the University of Havana. Following several years of full-time hospital work, Dr. Ortega received appointment, after competitive examination, as Associate Professor of Clinical Medicine in the University. He was later promoted to the head Professorship, to the Deanship of the School of Medicine, and to the Presidency of the University. At the time of his death, Dr. Ortega held the chair of Research Professor.

After World War I, Dr. Ortega pioneered in founding the "Ortega Clinic," with requirements for modern practice and group medicine similar to the best in the United States and Europe. His practice was very active with prominent patients and frequent consultations on difficult cases by his colleagues. All of his assistants are distinguished in their fields; some are Fellows of the American College of Physicians. He contributed greatly to the control of tuberculosis in Cuba, and served as president of the Cuban Society of Tuberculosis and of the National Board of Tuberculosis. His far reaching personality and outstanding capacity made him a great influence in Cuban medicine, and his accomplishments were recognized by his elections as president of the National College of Physicians, the Society of Clinical Studies, the Seventh National Medical Meeting, and the Section of Internal Medicine of the Eighth Pan American Meeting, among others.

Dr. Ortega was considered by local Fellows of the American College of Physicians to be the head of their group. He joined with others in Tampa in 1941, the year of his election to Fellowship, in establishing the College's growth in Havana.

Through his many medical papers, his teachings at the University, his success as a consultant, Dr. Ortega strongly influenced younger generations of physicians, impressing them with his knowledge of the best of European medicine and with his interest in the contributions of modern North American medicine. He was not only a very successful practitioner and man of science but a penetrating critic and a humanist with a clear philosophical mind. His passing has left a real sense of loss in the hearts of his patients, colleagues and pupils, but his spirit will certainly continue with them.

JOSÉ J. CENTURIÓN, M.D., F.A.C.P.,  
Governor for Cuba

### DR. CHARLES LEONARD OVERLANDER

Dr. Charles L. Overlander died December 16, 1948, at the age of 75. He was a self-effacing man of iron will, who had surmounted many difficulties and achieved success. He had contributed as a physician for 43 years to the health of the Boston community.

Dr. Overlander was Director of the Pathological Laboratory of the Brooks Hospital, Brookline, Mass., for 30 years. He graduated from the University of Ottawa, Ottawa, Kans., in 1896; later he endowed this University with a scholarship of \$10,000.00, for worthy students, particularly those who wished to enter scientific fields. He graduated from the University of Kansas School of Pharmacy in 1898. He received the Ph.B. degree in 1901 from the Sheffield Scientific School of Yale University, and then entered Harvard Medical School, from which he graduated cum laude in 1905. He subsequently interned at the Massachusetts General Hospital and the Children's Hospital. He was on the staff of the Boston Dispensary, 1908-1911, and was chemist to the Boston City Hospital from 1909 to 1917.

Dr. Overlander published articles in the Boston Medical and Surgical Journal, the Journal of the American Medical Association, the Interstate Medical Journal and the Lancet Clinic. He became a Fellow of the American College of Physicians in 1920, and was a member of the American Association for the Advancement of Science, the American Medical Association, American Society of Bacteriologists, Boston Bacteriological Club, Sigma Xi, Phi Rho Sigma, and the Harvard and Yale Clubs of Boston.

### MAJOR GENERAL GEORGE C. BEACH, JR. (MC), U. S. ARMY

George Corwin Beach, Jr., Assistant Surgeon General and Commanding Officer of the Army Medical Center, Washington, D. C., died November 18, 1948, at the Walter Reed General Hospital.

Dr. Beach was born in Topeka, Kans., October 28, 1888. He attended Washburn College and graduated in 1911 from the University Medical College of Kansas City. He interned in the University Hospital, Kansas City, Mo., and in 1912 became a lieutenant in the Medical Reserve Corps of the U. S. Army. In 1916 he was commissioned in the Medical Corps. His subsequent assignments included tours of duty at Fort Monroe, Va., Camp Greene, Charlotte, N. C., Letterman General Hospital, San Francisco, Calif., General Dispensary, Washington, D. C., Sternberg General Hospital, Manila, Fort Sherman, C. Z., and Europe. From 1935 to 1939, Dr. Beach was Chief of Medical Service of the Station Hospital at Fort Leavenworth, Kans. During the years 1939-46, he was Chief of Medical Service and Commanding Officer of the Station Hospital at Fort Sam Houston, Tex.

Major General Beach became a fellow of the American College of Physicians in 1935. He was a fellow of the American Medical Association and a member of the Association of Military Surgeons of the United States. He was a diplomate of the American Board of Internal Medicine.

#### REAR ADMIRAL ROBERT G. DAVIS (MC), U. S. NAVY, RETIRED

Rear Admiral Davis died on November 8, 1948, in San Diego, Calif. He was born in Indianola, Iowa, on May 29, 1883, and received his education at Simpson College (B.S., 1905) and Rush Medical School (M.D., 1909).

Dr. Davis entered the U. S. Navy in 1912 and advanced through various ranks to Captain in 1937. During his service, Admiral Davis served at the Naval Hospitals at Great Lakes, Ill., Las Animas, Colo., Puget Sound, Wash., and San Diego, Calif., as well as on board the *Wright*, *Langley*, *Aroostook* and *Saratoga*. He did pioneer work in establishing aviation medicine in the Navy, studying problems and methods abroad and engaging in research and instruction in this field.

During World War II, Dr. Davis served as District Medical Officer of the 16th Naval District and as Medical Officer in Command of the Naval Hospital and Medical Supply Depot at Canacao, Philippine Islands, where he was captured by the enemy Japanese forces January 2, 1942, along with members of his hospital staff. He was liberated from a Japanese prison camp on August 30, 1945, in Mukden, Manchuria, after having been interned for 43 months. Upon returning to this country in September, 1945, he was assigned to duty as a member of the Naval Retiring Board, San Diego, Calif., and was placed on the retired list on October 1, 1946. Among the many decorations that he held was the Legion of Merit for service in combat.

Admiral Davis became a fellow of the American College of Physicians in 1932. He was also a member of the American Medical Association, the Association of Military Surgeons of the United States, and of the San Diego Academy of Medicine.

#### DR. MARK STEVENS KNAPP

Dr. Mark Stevens Knapp of Fenton, Mich., died on November 11, 1948, at the age of 76. Dr. Knapp received his B.S. in 1895 and his M.D. in 1898 from the University of Michigan. Following graduation, he practiced for many years in Flint, where he was Chief of Medicine at the Hurley Hospital for some time. He was also a member of the Advisory Staff of this Hospital and the Women's Hospital. In 1920, he became a fellow of the American College of Physicians, being one of the earliest members in Flint. In 1934, he became a director of the Horace H. Rackham and Mary A. Rackham Fund, and was active in this work for two years, when Ménière's disease compelled him to retire. Since then he had lived in retirement in Fenton.

DOUGLAS DONALD, M.D., F.A.C.P.,  
Governor for Michigan

# ANNALS OF INTERNAL MEDICINE

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## THE PROTHROMBIN TIME IN DICOUMAROL THERAPY \*

By F. C. COLEMAN, M.D., *Des Moines, Iowa*

The identification of dicoumarol as the cause of sweet clover disease was made by Link in 1939. This disease is a hemorrhagic disease in cattle which have eaten spoiled sweet clover, and is due to a decrease in the prothrombin content of the blood. In 1941 Link reported the synthesis of dicoumarol. It could be prepared in large quantities at low cost. Within three months the first published report of its clinical use was made by Allen, Barker and Waugh. It is of therapeutic value in those diseases where intravascular clotting is present. These are, particularly, thrombosis and embolism following operation, trauma, infection or childbirth. Recently it has been used in congestive heart failure with venous or mural thrombosis and in coronary occlusion. Administration as a prophylactic measure against thrombosis following operation or childbirth has been recommended. In these cases the dicoumarol is started on the first to third postoperative or postpartum day.

The clotting of blood is thought to take place in two stages. In the first stage there is a conversion of prothrombin to thrombin in the presence of calcium and thromboplastin. In the second stage the thrombin unites with fibrinogen to form fibrin. Fibrin acts as the supporting framework for the platelets, red cells, and white cells present in a clot. Prothrombin is formed in the liver from vitamin K. Thromboplastin is present in the platelets and tissue juices, being particularly plentiful in the brain and lung. Calcium and fibrinogen are present in the blood plasma.

To prevent blood from clotting, at least one of the factors in the clotting mechanism must be removed or inactivated. We use potassium oxalate as an anticoagulant in the laboratory because it unites with the calcium of the plasma to form the inactive salt calcium oxalate. Thus, no calcium is free to assist in converting the prothrombin to thrombin. Blood does not

\* Presented before the State Divisional Meeting of the American College of Physicians in Des Moines, Iowa on September 27, 1947. Received for publication February 12, 1948. From the Department of Pathology, Mercy Hospital, Des Moines, Iowa.

clot normally inside the blood vessels because of the movement of the circulation, the absence of free thromboplastin, and the presence of small quantities of antithrombin and heparin in the plasma. When conditions are such that intravascular clotting might occur it can be prevented by dicoumarol administration. Dicoumarol prevents intravascular clotting by decreasing the prothrombin content of the plasma. This is done by inhibiting its formation in the liver. None of the other functions of the liver are interfered with. Although prothrombin formation is stopped almost immediately, the prothrombin already present in the plasma must be exhausted. This accounts for the 24 to 48 hour lag in effect of the dicoumarol on blood clotting. It is obvious that the dosage of this drug must be controlled in some way. Since its action is to decrease prothrombin, the logical step would be to measure the amount of prothrombin present in the plasma. This cannot be done by exact chemical methods such as those used in determining the concentration of calcium or phosphorus. The clotting time of blood, however, is proportional to the amount of thrombin present when calcium, thromboplastin and fibrinogen are present in adequate amounts. Under normal conditions the amount of thrombin formed in turn is proportional to the amount of prothrombin present in the blood. All methods for determining the prothrombin time, then, are based on measuring the clotting time when calcium, thromboplastin and fibrinogen are present in adequate amounts. Approximately three-fourths of the clotting time is taken up in the conversion of prothrombin to thrombin, and the other one-fourth in the formation of fibrin from thrombin and fibrinogen.

Methods for determining the prothrombin time may be divided into two groups: (1) Those performed on plasma; (2) Those performed on whole blood.

Those performed on plasma include the Quick method and all of its modifications. Oxalated venous blood is used. An exact amount of calcium is then added to the plasma, as well as an excess of thromboplastin. The thromboplastin used may be of two types. In the original Quick method thromboplastin prepared from rabbit brain was suspended in normal saline. The clotting time of normal plasma was 18 to 22 seconds. A decrease in prothrombin content was indicated by an increase in the time necessary for clotting to take place. This method gave rise to the term "prothrombin time," for the results actually were expressed in terms of seconds.

Subsequently, Quick extracted the rabbit brain with acetone. This gave a much more potent thromboplastin which produced clotting in normal plasma in 11 to 12 seconds. The results are reported in terms of prothrombin concentration rather than in seconds. To calculate the prothrombin concentration normal plasma is diluted serially with saline from 100 per cent to 5 per cent. As the plasma is diluted the prothrombin content is decreased. Prothrombin determinations are then made on the normal plasma and all of the dilutions. The results are expressed graphically.

From this graph the prothrombin content of the patient may be expressed in terms of the dilution of normal plasma containing this amount. This is known as the prothrombin concentration. Quick also devised a formula by which the same results may be obtained without using the graph.

Stewart and Pohle modified Quick's method slightly by varying the amount of calcium. By using acetone extracted rabbit brain as a source of thromboplastin they were able to get a clotting time of as low as 10 seconds on normal plasma. The results are expressed in terms of prothrombin concentration just as in the second Quick method. Both methods have the disadvantage of showing considerable variation if an error of even one second is made in recording the clotting time.

The Magath modification of the Quick method is used at the Mayo Clinic. Saline suspensions of thromboplastin prepared from rabbit brain are used, but each batch is carefully standardized. Those thromboplastins which give a normal clotting time of 17 to 19 seconds are saved. These are then set up against serial dilutions of normal plasma. Only those which give a clotting time of 27 seconds with the 30 per cent dilution, 35 seconds with the 20 per cent dilution, and 60 seconds with the 10 per cent dilution are used. Since by this method a 20 per cent prothrombin concentration is considered to be optimum in dicoumarol therapy, 35 seconds is used as the guide for ordering or withholding the drug.

The Fullerton modification of the Quick method utilizes viper venom as a source of thromboplastin instead of rabbit brain. The results are reported in the same manner as in the second Quick method. In the Link modification of the Quick method a 12.5 per cent dilution of plasma is used instead of whole plasma.

There are two methods in which the determinations are performed upon whole blood. The one most commonly used is the Smith bedside technic. This method is technically the easiest to perform, and, as the name implies, can be done at the bedside of the patient. Thromboplastin prepared from ox lung is diluted with normal saline so that when added to normal blood it will clot in 25 to 30 seconds. No calcium is added, the calcium of the plasma being considered adequate. Whole venous blood is added to the thromboplastin and the tube tilted back and forth until clotting takes place. The same procedure is then repeated on a normal control. The clotting time of the control in seconds, divided by the clotting time of the patient in seconds, gives the prothrombin time of the patient in percentage of the normal control. This method has been criticized as being too insensitive for use in controlling dicoumarol therapy. These criticisms are based on the fact that whole blood is used rather than plasma. Since prothrombin is present in the plasma only, variations in the hematocrit will alter the amount of prothrombin in a measured quantity of blood.

The micro method of Kato and Poncher is similar to Quick's method except that a drop of oxalated blood secured from a finger puncture is used

instead of oxalated plasma. The test is always performed at room temperature. The results are expressed in terms of the prothrombin concentration.

Other methods which have been described include the Smith two-stage technic and the method of Dam and Glavind. These are not in clinical use.

It is obvious that marked confusion may arise in the interpretation of a prothrombin report unless one knows the method which has been used. As an example—a patient with the same amount of prothrombin in the blood might be reported as having: (1) A prothrombin time of 25 seconds (Quick's method, original); (2) A prothrombin of 60 per cent expressed in terms of prothrombin concentration (Stewart and Pohle); (3) A prothrombin of 45 per cent expressed in terms of prothrombin concentration (Magath modification of Quick's method); (4) A prothrombin of 72 per cent of normal (Smith bedside technic). How then are we to know what the prothrombin report means when it is noted on the patient's chart? It is essential that one method be standard in each laboratory and that the Staff knows the method which is being used. It is extremely important that only one technician be assigned to perform prothrombin determinations. For this reason we do not run them on Sundays except in cases of emergency. Even with the same technicians running the tests the technical error is around 10 per cent.

A good schedule to follow on any patient who is to receive dicoumarol is as follows: Have a prothrombin determination made. Then, give 300 mg. of dicoumarol by mouth. Guide further therapy with daily prothrombin determinations. When the prothrombin is above 20 per cent of normal using either the Quick method or the modifications of Magath, Stewart and Pohle or Kato and Poncher 100 to 200 mg. of dicoumarol may be given. If the prothrombin is less than 20 per cent it should be withheld. If the prothrombin is less than 40 per cent of normal using the Smith bedside technic, dicoumarol should be withheld. If it is above 40 per cent, 100 to 200 mg. may be given.

The response of the patient to dicoumarol varies considerably. Vitamin C deficiency enhances the effect of the dicoumarol. Salicylates should never be given at the same time as dicoumarol because they also enhance the anti-coagulant effect. This is particularly true of aspirin. Dicoumarol is chemically related to salicylic acid and a dicoumarol-like action may be produced by administration of large doses. Patients with severe renal or liver damage should never receive dicoumarol as the anticoagulant effect is exaggerated. Caffeine, theophyllin and theobromine on the other hand tend to nullify the action of dicoumarol. This is probably due to a stimulation of the liver to produce prothrombin. The tendency of these drugs to increase the clotting ability of the blood is of importance in coronary disease. Here thrombosis may be accelerated.

Heparin is frequently started at the same time as dicoumarol and con-



tinued for the 48 hour period necessary for dicoumarol to take effect. This is done because most emboli come from thrombi which are less than 48 hours old. Since the dicoumarol is not given to resolve thrombi already formed but to prevent thrombus propagation and embolism this appears to be a rational procedure. Heparin seriously interferes with prothrombin determinations, however, and these should never be done within three hours after heparin has been given. The effect of heparin has disappeared after this time and true readings will be obtained.

Dicoumarol therapy would be very dangerous if there were no way to counteract its effects. Recent studies have shown that the prothrombin content of the blood may be returned to normal within 24 hours by administration of large doses of vitamin K intravenously and by the administration of whole blood transfusions. The dosage of vitamin K usually recommended is 60 mg. of menadione bisulfite intravenously every eight hours.

The prothrombin content of bank blood decreases rapidly so that it may be 50 per cent in blood a week old. Fresh blood, therefore, is preferable to bank blood. If bank blood is used, it should not be more than 48 hours old. Since vitamin C deficiency enhances the dicoumarol effect, large doses of vitamin C should be given when prothrombin content is being returned to normal. These measures are applicable to patients who show excessive bleeding or in those on whom surgery is necessary.

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# EARLY DIAGNOSIS OF CARCINOMA OF THE STOMACH \*

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CARCINOMA of the stomach continues to be the foremost cause of cancer deaths. Despite improvements in diagnostic and surgical technics, five year survival rates have not been altered appreciably<sup>1, 2</sup> in the past 10 years, and there is no reason to believe that they will be in the future.

The increased use of roentgen-ray and gastroscopic examination have led to more frequent diagnoses of gastric carcinoma but not to increased cures. All of our present diagnostic methods depend on the patient presenting himself because of symptoms. Due to the silent nature of the disease, the symptoms are rarely severe enough to bring the patient to the physician until the tumor has become widespread.

The lesion is present for an unknown period before the patient becomes aware of any physical derangement. The earliest symptoms fail to form a recognizable syndrome. If the physician depends on established diagnostic criteria, he will rarely discover an early malignancy of the stomach.<sup>3</sup>

In an effort to discover any findings that might lead to earlier diagnosis, 109 cases of gastric carcinoma diagnosed at the State University of Iowa Hospitals in 1941 and 1942 were analyzed. Search was made for any information that might lead to the use of roentgen-ray examination of the stomach earlier in the course of the disease, and also for any findings that might indicate resectability prior to operation or might aid in predicting survival.

## ANALYSIS

*Sex and Age Incidence.* Of the patients with gastric carcinoma that came to the State University of Iowa Hospitals in 1941 and 1942, 91 were men and 18 were women, the ratio being five to one. Although females composed only 16 per cent of the group, they made up 33 per cent of the survivors over two and a half years. The majority of cases occurred between the fiftieth and seventieth years.

*Presenting Symptoms.* The outstanding features of the presenting symptoms were their vagueness and insidious onset. None of the first symptoms suggested the serious nature of the disease, and with few exceptions they were compatible with those of so-called functional disease of the gastrointestinal tract.

Vague epigastric distress was the most common presenting symptom and ranged from "bloating," "fullness," or "indigestion" to actual pain. Weight

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loss frequently antedated all symptoms but was so gradual in development that its significance was not apparent until late. Weakness was commonly reported. Several patients described decreased gastric capacity, saying that they "couldn't eat much at a time."

Symptoms simulating the ulcer syndrome, including relief of pain on taking food or alkalies and tenderness to palpation, occurred in 11 cases.



FIG. 1. A film of the abdomen taken five hours after the ingestion of barium demonstrates the delicacy and uniformity of the mucous membrane markings in the normal small bowel. The even distribution of the barium and regular caliber of the small bowel is shown.

This was not necessarily associated with an ulcer type of defect. Constipation was the presenting symptom in about 15 per cent of the cases, sometimes occurring in the absence of epigastric distress. Diarrhea was frequently reported.

The textbook symptoms of anorexia and vomiting were almost com-

pletely absent until late in the disease. Five of the patients reported a good appetite. Other presenting symptoms were sore tongue, dysphagia, back pain and nervousness.

*Duration of Symptoms.* The average duration of symptoms was 11 months with extremes of four weeks and five to six years. The duration of symptoms was no indication of the extent of tumor growth. Of 23 cases with as short a history as three months or less, 17 had wide dissemination of the lesion, making curative surgery impossible. Representative cases are included in table 1.

TABLE I  
Extent of Disease in Cases with Short History

Age of Patient	Sex	Duration of Symptoms	Presenting Symptoms	Extent of Disease
51	M	4 weeks	Regurgitation shortly after eating. 30 to 40 lb. weight loss.	Cardiac end of esophagus and stomach.
59	M	10 weeks	"Flu" and diarrhea. Black stools.	Involvement of pylorus with extensive peritoneal seeding.
36	M	2 months	Pain in epigastrium. Retention of food. 13 lb. weight loss.	Virchow's node. Palpable epigastric mass, large gastric filling defect.
69	M	2 months	Gas, bloating, epigastric pain and fatigue.	Marked involvement in pars media. Implants in mesentery and lymph nodes.
58	M	2 months	Stomach distress. 10 lb. weight loss. Decreased gastric capacity.	Distal half of stomach infiltrated. Omental and retroperitoneal nodes.
71	F	2 months	30 lb. weight loss. Weakness and fatigue.	Elevated neoplasm 2½ inches in diameter with early ulceration. No nodes.
61	M	3 months	Discomfort, bloating.	Widely disseminated beyond regional nodes and involvement of pylorus and pars media.
44	M	3 months	Weakness and weight loss.	Lung, liver and peritoneal metastases. Filling defect in pylorus.
56	M	3 months	Epigastric distress; bloating.	Filling defect involving antrum. Metastases to posterior cul de sac.
71	M	3 months	Vomiting, weakness and 25 lb. weight loss.	Filling defect of lower two-thirds of stomach. Virchow's node.

*Physical Findings.* Of the physical findings, cachexia was most frequently reported, being described in over 64 per cent of the cases and probably present in many more. Epigastric masses were palpable in but 35 per cent of the patients although some may have been masked by rigidity of the abdominal wall in an additional 20 per cent. Paleness was noted in 23 per cent of the cases. The epigastrium was tender to palpation in 18 per cent. Virchow's nodes were felt in 6 per cent; Blumer's shelf in 14 per cent; abdominal distention or ascites in 4 per cent with one case each of pleural and osseous metastasis; making a total of 26 per cent with evidence of widespread

neoplastic metastasis on entrance examination. The liver was palpable in only 15 patients.

*Survival Related to Treatment.* A curative operation was attempted in every case in which the involved portion appeared resectable. This included cases with extension to the pancreas, mesocolon and esophagus, in addition to those limited to the stomach and regional lymph nodes.

Sixty-six patients, or 62 per cent, were operated upon at this hospital with an overall surgical mortality of 15 per cent. Surgical deaths were excluded when calculating average survival periods.

Thirty-one per cent of those patients surviving a curative procedure were still living after five years.

Those surviving a palliative operation lived about two months longer than those patients who had only an exploration or no surgical treatment.



FIG. 2a. A film taken shortly after ingestion of barium shows a nodular, exophytic filling defect at the pars media. The mucosal pattern of the duodenum and jejunum is well demonstrated and appears normal.



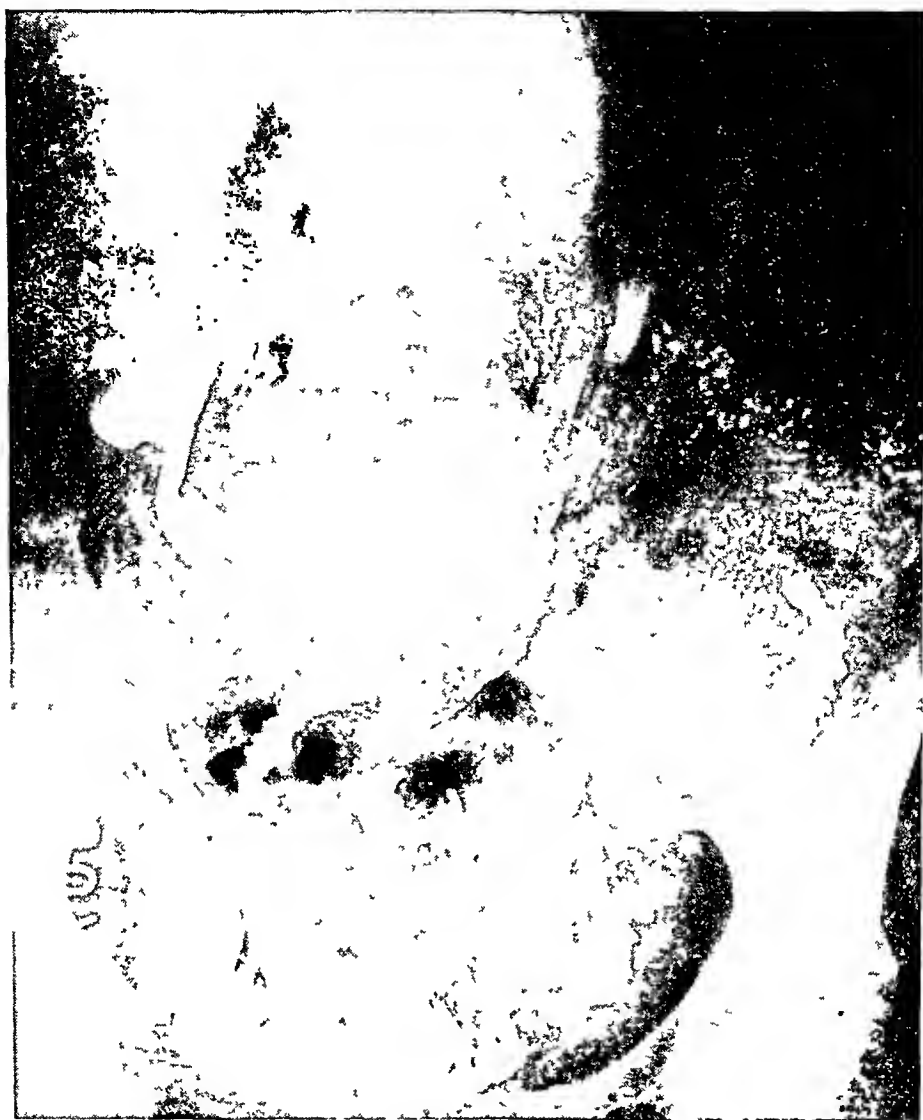


FIG 2b Five hours after the ingestion of barium, the head of the meal has advanced to the distal ileum, portions of it lying scattered through the jejunum and clumped in the proximal ileum, which shows hypersegmentation. The mucosal folds in the proximal ileum appear coarsened, due to edema incident to hypoproteinemia.

One patient, diagnosed by roentgen-ray and gastroscopic examination as having carcinoma of the stomach, refused operation and remained alive and well for over five years. Review of his films suggests that the correct diagnosis was giant rugal folds, and the case was excluded from the series.

For the group as a whole regardless of treatment, 77 per cent were dead in one year, and 92 per cent by three years. Those alive at this time continued to be alive and well at five years. The five year survival rate of 8 per cent approximates the figures reported by most American clinics.

*Survival Related to Degree of Involvement.* At operation, the lesion was found to be limited to the stomach in only 11 patients and these had an

average survival of 53 months, seven of the patients being still alive and showing no evidence of recurrence after more than 60 months. The lesion was limited to the stomach and regional nodes in 15 patients or 14 per cent. Only two of these patients are alive after five years and an additional one could not be traced after two years. Fifty-eight per cent were known to have widespread metastasis and local extension.

TABLE II

Surgical Evidence of Disease Compared with Clinical Findings

Widespread Metastases		26%
Virchow's node	6%	
Blumer's shelf	14%	
Ascites	4%	
Pleural metastasis	1%	
Osseous metastasis	1%	
Clinical Evidence of Limitation to Stomach and Regional Nodes		74%
Surgical Evidence of Limitation to Stomach and Regional Nodes		24%

*Laboratory Findings.* Anemia was a prominent finding, as was depression of the plasma protein levels. This occurred in spite of a masking effect produced by chronic dehydration. Mellors and Abbott<sup>4</sup> have shown that the circulating plasma volume is decreased in the course of this disease. The values were calculated on admission, before the patient had time to become hydrated. Nevertheless, the hemoglobin was below 11 grams in 63 per cent

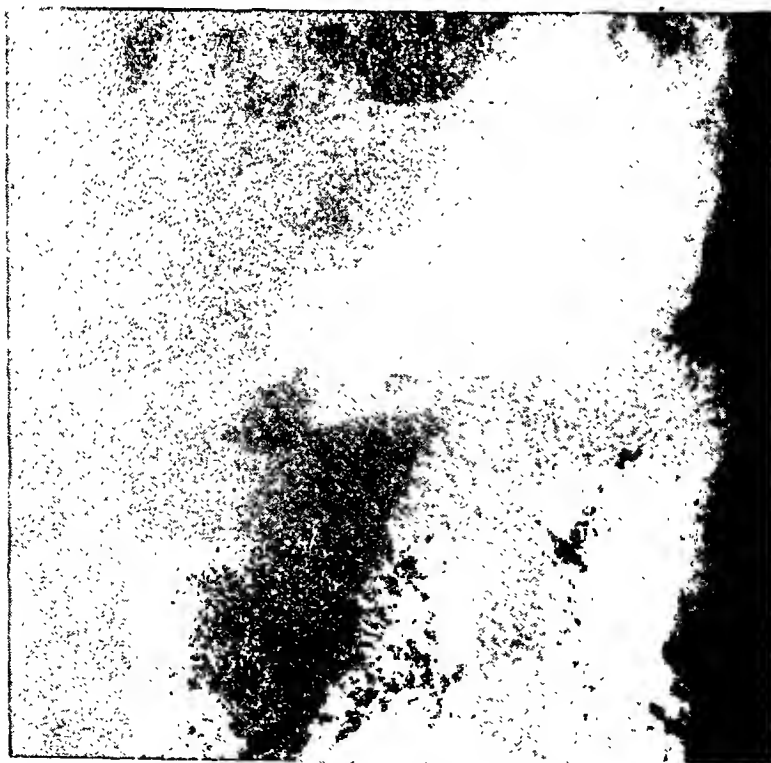


FIG. 3a. A film taken shortly after ingestion of barium shows an irregular filling defect involving the antral and pyloric portions of the stomach. The duodenal and jejunal mucosal patterns appear normal.



FIG. 3b. A film of the abdomen taken five hours later shows the major portion of the meal in the distal ileum. Some of the barium remains in the proximal ileum, where it exhibits hypersegmentation. The caliber of the ileum is variable, some of the segments being dilated.

of the cases, and the red cell count below 3.8 million in 52 per cent. One of the most consistent findings was depression of the plasma protein levels, the total protein being below 6.0 grams in 78 per cent; plasma albumin, 4.0 grams or less in 100 per cent; and plasma globulin below 2.5 per cent in 65 per cent.

The anemia was of variable types, and not limited to the hypochromic normocytic type typical of chronic minor hemorrhages. Many of the red cells displayed poikilocytosis and anisocytosis. Rhoads and his group<sup>5,6</sup>

feel that the anemia associated with gastric carcinoma represents a blood dyscrasia based on a failure of transfer or storage of a gastric anti-anemic factor, into the liver. Liver damage seen in hypoproteinemia also contributes to poor blood regeneration:

TABLE III  
Survival Related to Treatment

Procedure	Cases	% Distribution	% Surgical Mortality	Average Survival in Months
Curative	29	27	10	35*
Palliative	13	12	23	8
Exploratory	26	23	15	6
No surgery	41	38	—	5

\* Nine patients alive and well 60 months following operation.

Anacidity and hypoacidity after histamine were frequent findings, being present in 79 per cent of the cases tested. Some cases had free acid, even in excessive amounts. This was true of the smaller lesions.

*Roentgen-Ray Findings.* In our experience, like that of others,<sup>7</sup> the roentgen-ray examination was the most definitive of all diagnostic methods. One hundred and five of the cases received an upper gastrointestinal examination, and carcinoma of the stomach was diagnosed or suggested in 96 patients or 91 per cent. Of the nine errors, two were diagnosed as benign ulcers, and one lesion was described as carcinoma in the duodenal loop rather than the stomach. The other six were called normal stomachs.

Most of the lesions occurred in the antrum and occupied both lesser and greater curvatures. Carmen's meniscus sign was observed in only four of 96 examinations. Foreshortening of the lesser curvature was a frequent observation.

TABLE IV  
Survival Related to Degree of Involvement

	Cases	Per Cent Distribution	Average Survival in Months	5 Year Survivals	Per Cent
Limitation to stomach	11	10	53	7	64
Limitation to regional nodes	15	14	22	2	13
Widespread metastases and local extension	63	58	4	0	0
Unknown degree of involvement	20	18	8	0	0

The roentgen-ray appearance of a lesion could not be used as an index of resectability. Large filling defects sometimes had limited extragastric extension, while small ones were found to be widely disseminated at operation.

The small bowel displayed disturbed motor physiology in 58 per cent of the cases, as judged from films taken immediately and five hours after the

ingestion of barium. The duodenum and proximal jejunum always appeared normal but clumping, segmentation, and mucosal edema were observed in the distal jejunum and ileum. Transit time was ordinarily normal.

Whether the small bowel disturbance was the cause or the effect of avitaminosis and hypoproteinemia associated with malignancy is a matter of conjecture. It is known that vitamin B complex is poorly absorbed in the presence of decreased gastric acidity.<sup>8</sup> Lack of vitamin B is one cause of disturbed small bowel pattern, perhaps leading to failure of absorption of essential food elements. Mucosal edema due to hypoproteinemia adds to the deranged small bowel function. The relationship of this finding to the anorexia and cachexia of malignant disease should be investigated.

### DISCUSSION

This study indicates that in order to cure a reasonable number of patients, gastric resection must be done while involvement is limited to the stomach. Extension beyond this, even when limited to the regional nodes, causes a sharp drop in survival rate.

While our present diagnostic methods are capable of diagnosing gastric malignancy at a curable stage, the patients rarely present themselves at such a time. There were no symptoms that could be correlated to the curable type. With one exception, every patient with physical findings beyond weight loss was dead in five years; this one patient had a palpable movable epigastric mass.

It is evident that carcinoma of the stomach must be found while it is still asymptomatic. Dailey<sup>9</sup> and St. John<sup>10</sup> have conducted wide scale roentgen-ray screening experiments on symptomless males in the cancer age group. Dailey failed to find any gastric carcinoma in 500 men over 45. St. John found the incidence of gastric malignancy to be 1.24 cases per thousand, which is too low an incidence to make this type of examination practical as a screening procedure.

In order to select a group more likely to have a higher incidence, Rigler<sup>11</sup> limited his screening examinations to patients known to have possible precursors of gastric carcinoma—achlorhydria, a chronic gastritis, pernicious anemia, gastric polyps or a family history of carcinoma of the stomach. Wangenstein<sup>12</sup> followed a group, using the same indications and in addition, examined all patients with occult blood in the stools, unexplained anemia below 11 grams of hemoglobin, lingual mucosal atrophy or severe pyorrhea alveolaris. Both investigators found carcinoma in percentages far beyond the natural occurrence. Yet, though these cases were discovered earlier, only a few were still at a stage of development at which a cure was possible. Further, a complete physical and laboratory examination is necessary in order to select suitable candidates for investigation, making such methods too expensive and time consuming to extend to the entire cancer vulnerable popu-

lation. Routine photofluorographic examination of the stomach is being tried experimentally but it is unlikely that any but the larger lesions will be discovered in this manner.

The Papanicolau smear technic<sup>13</sup> has been adapted to gastric aspirations and can be used as an adjunct in all cases having gastric analysis or gastroscopy. Cell detail is surprisingly well preserved despite exfoliation into digestive juices; however, even in Papanicolau's hands, a high percentage of cases were missed because of poor cell preservation and the failure of scirrhous carcinoma to shed cells. Further, the requirement of gastric aspiration makes this method undesirable as a screening procedure.

Present methods are not adapted to the diagnosis of carcinoma of the stomach at a stage at which the majority of cases can be cured. A new medium of diagnosis must be discovered before five year survival rates can be increased.

Lacking new methods, the present methods should be used more extensively. A roentgen-ray examination should be given to every patient with even the vaguest gastrointestinal complaints. All asymptomatic individuals known to have possible precursors of gastric cancer should receive roentgen-ray examinations twice yearly.

All gastric ulcers, and cases of pyloric obstruction should be examined gastroscopically. Gastric ulcers which fail to heal on adequate medical management should be regarded with deep suspicion. Partial healing cannot be considered evidence of the benign nature of an ulcer, as malignant ulcers can fill in, as shown by Palmer and Humphreys,<sup>14</sup> and Eusterman.<sup>15</sup> Allen<sup>16</sup> reports that during a 10 year period at the Massachusetts General Hospital, 14 per cent of the patients given a medical treatment for benign ulcer actually had a malignancy, as proved by surgical and autopsy findings.

#### SUMMARY AND CONCLUSIONS

1. The innocuous nature of presenting symptoms of carcinoma of the stomach is emphasized. The delay in diagnosis after onset of symptoms averaged 11 months.

2. The physical findings are misleading, in that they suggest that the extent of the lesion is far more limited than it is found to be upon exploration.

3. Roentgen-ray diagnosis was accurate in 91 per cent of the cases.

4. A five year survival rate of 8 per cent is reported. Cures occurred almost exclusively in cases with involvement limited to the stomach, despite the use of an attempted curative operation in more extensive types.

5. Depressed plasma protein levels, particularly albumin, and an abnormal small bowel pattern are frequent findings.

6. The duration of symptoms and the roentgen-ray appearance of the lesion could not be correlated to the extent of involvement or survival period.

7. None of the present diagnostic methods are practical in increasing the detection rate of carcinoma of the stomach at a stage in which a reasonable chance of cure exists.

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## FACIAL PAIN \*

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FOR some time we have been amazed at some of the unusual concomitants of dental disorders, especially with reference to the cause of pain so frequently seen in and around the face. The subject has been copiously reviewed as "Atypical Face Pain" by McElin and Horton,<sup>1</sup> and Glaser,<sup>2,3,4</sup> to whose papers and bibliographies one is referred. These authors have in the main dealt with the pathways by which pain is referred, and have attempted to treat the pain by an attack on the pathway, while Kelly and Langheinz<sup>5</sup> appear to have made a step in attacking the cause of the pain, though their method seems quite complicated.

The following cases are presented:

*Case 1.* A 28 year old female dental assistant was seen because she had become alarmed by very severe pain in the right zygomatic region six weeks previously. The pain had not been relieved by analgesics. After roentgenogram the right upper wisdom tooth was claimed to be impacted and was removed. This relieved the pain. At the time of physical examination no abnormalities other than an absent lower right six year molar and a secondary anemia were noted. Roentgenograms of the sinuses and teeth revealed no roentgenologic abnormalities. She was advised to have a fixed sanitary bridge to replace the absent six year molar (which advice was not followed), and after the correction of the anemia was not seen for eight months. At this time she had a sudden return of her severe pain associated with persistent vomiting. The sinuses transilluminated well and there was no tenderness over the sinuses. It was apparent that the lower right 12 and 18 year molars had tilted mesially, so that the distal cusps were higher than the remainder of the respective separate teeth, also higher than the occlusal line, and in forward motion of the mandible these distal cusps exerted a cam action against the similar cusps of the upper molars. She stated that she did most of her chewing on the right side. The lower two right molars were ground so that the right side of the jaw occluded simultaneously with the left side of the jaw, and her pain has not reappeared.

*Case 2.* A 78 year old white female physician was scratched in the nasolabial fold by a cat. Within 48 hours the area showed an extensive, weeping, spreading, impetiginous lesion. Self-medication for several days was unavailing. A dermatologist was consulted, but no improvement occurred. Because of bleeding gums and purulent exudate at the gingival margins, she consulted one of us (W. L.), who noted recession of spongy, easily bleeding gums in the central areas, where malocclusion was forcing the closed lower incisors and cuspids against the uppers. These lower teeth were ground sufficiently to allow clearance on occlusion. The following day the face was much improved, and by the third day was completely healed. Except for gingival recession the gums returned to normal, and the bleeding and purulent exudate ceased with this relief of abusive stress.

*Case 3.* A 38 year old white female, the wife of a physician, saw her otolaryngologist for severe pain in the right ear. After careful study the otolaryngologist

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told her there was nothing abnormal within the scope of his specialty, but that she should see her dentist. Fixed sanitary bridges had been placed in the lower jaws to replace absent six and 12 year molars, and on examination the right bridge was found to have a high spot which struck the upper 12 year molar prematurely on occlusion. This high spot, about 1/1000 inch, was ground off, and the patient has had no recurrence of the pain in her ear for four years.

*Case 4.* A 35 year old physician had marked recession and periodic bleeding of the gums for some years. Massive doses of vitamins C and K had stopped the bleeding intermittently during medication, but had not permanently corrected either the bleeding, recession, or sponginess of the gums. He had seen several dentists as he moved around the country in pursuit of his training. At age 21 his lower left six year molar had been removed. When seen, the gap between the lower left fifth and seventh teeth had narrowed to 7 mm., and a gap had appeared between the lower left third and fourth teeth measuring 4 mm. The lower central incisors were crowded out of line, twisted, and overlapping. His teeth were extremely sensitive. At no time had he ever been advised to have the lower left six year molar replaced. Marked malocclusion was present in the lower left jaw because of depression by mesial movement of the molars and bicuspsids.

A fixed sanitary bridge was inserted. The upper left and lower right six year molars were loose, had marked recession of the gums and alveolar processes (roentgenograms), and attempted correction by the procedure to be outlined allowed only further extrusion of these two molars. These were removed and fixed sanitary bridges were inserted. His occlusion was corrected and the pyorrhea and bleeding improved markedly, except in the area of the lower left second and third teeth, which were found to grind against his upper left central incisor when asleep. These three teeth were ground further to allow clearance (even when asleep) and improvement was noted. Pressure of the tongue against the lower central teeth, a habit acquired in blowing smoke rings, was causing considerable stress on these teeth, and further improvement in the condition of the gums was noted when the habit was broken. However, the gap between the lower left third and fourth teeth has increased, and there is further crowding and torsion of the lower left incisors; as they move and are subject to abnormal stress and strain, they are ground to allow clearance, and it is hoped that they will soon stop moving.

*Case 5.* A 30 year old white female was admitted to the hospital with severe cardiac decompensation, rheumatic heart disease, and marked valvular deformities. During convalescence she began to note annoying pain which, though momentary, was severe and stabbing, starting in the neck and radiating up into the face in the infraorbital regions. The teeth appeared in good condition except for a small cavity in the lower right six year molar. There did not appear to be any recession of the gums or the alveolar processes; roentgenograms of the teeth and sinuses were normal. Because of her general condition it was not deemed advisable to repair the six year molar at this time, and the pain was controlled ineffectively with salicylates. Shortly after returning home to continue her convalescence the gum around the upper left six year molar began to bleed on brushing, and she complained that it was sensitive. No caries could be found in this tooth and soon the gum began to recede. Because her heart condition was progressively deteriorating it was not felt advisable to do anything to the teeth except to continue the program of analgesics. However, the pain increased in severity, duration and frequency, and required codeine for relief. When codeine was no longer sufficient to control the pain without completely destroying her appetite and bowel habits, it was decided to remove the upper left six year molar as the simplest procedure in the home. This was done with relief of the abnormal stress and strain between the two left six year molars, and there was a cessation of the pain for the remaining seven months of her life.

*Case 6.* A 60 year old white female nurse had severe osteo-arthritis of the right hip as a late result of trauma as a young woman. This was becoming progressively more crippling. In February 1947 she developed a corneal opacity in her left eye. She was seen and treated locally by her ophthalmologist. From February to July 1947 she had a recurrence of corneal opacities in either eye on seven separate occasions, each recurrence becoming more severe and more resistant to treatment. In July, when she had a corneal opacity with iritis in the right eye, she was seen by an internist who noted the following oral condition:

The fifth left upper tooth had been removed the year previously because of crowding in the upper incisor region, and the upper left sixth, seventh, and eighth teeth had angled forward to close the gap. There was extreme recession of the gums of all upper molars. The lower molars had been replaced by a removable bridge which clasped on to both lower fifth teeth. The patient complained of some irritation of the gum below the left side of the removable bridge. There was marked recession of the gum of the lower left fifth tooth. The lower remaining teeth were bearing considerable weight and were badly worn. The gums bled easily and the teeth were quite loose.

It was advised that the bridge be removed and left out. Within 12 hours there was marked improvement in the iritis and the corneal opacity was definitely smaller. In 36 hours the opacity had disappeared.

Roentgenograms showed excessive alveolar destruction throughout, and a peri-apical abscess at the base of the lower left fifth tooth. With the exception of two teeth, there was so little bone holding the teeth that, at her age, it was advised she have all the teeth removed. This was done, at which time she had massive doses of penicillin prophylactically, and since then there has been no recurrence of corneal opacities or iritis. Incidentally, her osteo-arthritis is much less painful and considerably less crippling.

*Case 7.* A 25 year old white female housewife was seen for a complaint of pain in the right eye of three months' duration. Associated with this at times was pain which began at the vertex and spread down over the whole right side of the head and neck. The progressive intensification of symptoms was beginning to cause insomnia. Aspirin, which had been beneficial in the beginning, was losing its efficacy. She admitted to chewing solely on the right side of the jaw. On examination the gums were found to be in excellent condition, one-sixth of the right upper cuspid was worn off, the lower left bicuspid was displaced buccally and were not bearing much, if any, weight. The weight was borne mainly by the teeth on the right side.

The right bicuspid and molars were ground slightly, so that the two sides of the jaw were balanced to bear weight equally, and to occlude simultaneously. She was warned that she had a habit of grinding the right cuspids, and she was discovered to have a sliding lateral motion on the right cuspids when concentrating on problems. She corrected her grinding habit, pain in the right eye ceased completely, and in a few days the other symptoms disappeared. The cessation of abusive stress has obviated any need for further treatment in seven months.

## DISCUSSION

The procedure used in this method of treatment of pain and pyorrhea is very simple. Red carbon paper, coated on both sides, is applied between the teeth and the patient is asked to bite normally, i.e., as he would were he chewing meat. Any abnormally high spots will be colored red. These can then be removed by a small grindstone. Care must be exercised to check the whole mouth and to balance the two sides, so that they occlude simul-

taneously. Also, care must be exercised, if much grinding is necessary on the "grinding" teeth (the molars and bicuspid), to be sure that the "cutting" teeth (the incisors and cuspids) do not become "weight-bearing" teeth and subject to abnormal and excessive stress and strain for which they were not designed. When the "grinding" teeth, which are the normal "weight-bearing" teeth, are worn or ground excessively there is an increased closure of the temporomandibular joint, and the lower incisors are brought further forward and up, so that they will occlude against the posterior surfaces of the upper incisors. This in turn subjects them to "weight-bearing."

Occasionally one will note a very powerful cam action between opposing cusps, especially if there be any lateral motion of the jaw during occlusion, which can subject the involved teeth to excessive strain; often under these conditions there will be found excessively tender teeth. In like manner, excessive stress can be applied to teeth if they be struck continually in a plane other than the longitudinal axis of the tooth, e.g., when the tooth has angled over to fill in a gap following the removal of another tooth. This pressure is then maximally exerted at the weakest point of the tooth at the gum line. The root of the tooth is firmly imbedded, and the force is applied by leverage at the weak fulcrum (gingival margin). This in turn causes an abrasion and laceration at the gingival margin which is being continually traumatized. Teeth so exposed to continuous abusive stress can become exquisitely tender, so much so that the patient is sure that caries is present. The proof of sensitivity being caused in this way can be shown by four facts: (1) the frequent absence of any caries; (2) the extreme sensitivity of the tooth to the application of metal, metallic salts, or pressure above the enamel; (3) the extreme sensitivity of the tooth to any drilling, brushing, or sweets; and (4) probably the most conclusive proof, the disappearance of the sensitivity of the tooth and all portions thereof when the abusive stress has been removed.

Many mouths will be seen which are very dirty in the absence of proper dental hygiene, in which no pyorrhea is present. The reverse is equally true where the hygiene by the patient and attention by the dentist are scrupulously observed. The answer, we feel, lies in not traumatizing the abrasion and laceration. When an external injury interrupts the continuity of the integument, every effort is made to relieve it from every possible irritation or stress by complete immobilization. The same basic principle should be applied to the teeth and their supports; the teeth are not made of rubber, but when subjected to abusive stress will impart the stress to their supporting structures and incidentally irritate the nerve supply.

If physicians and dentists will pay attention to the little signs of spongy, bleeding and receded gums, purulent exudate and calcareous deposits at the gingival margins, malocclusion and absent teeth, they will often discover minor defects in the mouth which, with the application of good preventive medicine, may be corrected easily at the time. If allowed to progress they may become of major importance and lead to extensive dental repairs.

Moreover, they may be associated with unusual and often puzzling and distressing symptoms of pain, sensitive teeth, earache, temporomandibular crepitation and pain, pyorrhea, iritis, and other infection. In this connection we wonder if there might be a relation between abusive stress of the teeth and trigeminal neuralgia.

We are not attempting an elucidation of the pathways by which pain is referred from the teeth to various portions of the face and head in these bizarre cases. The reader is referred to the various texts on neuro-anatomy and neurophysiology. We feel that in at least some of the cases of face pain there is a definite relationship to the teeth, and that by very simple procedures this can be corrected. We do not feel that extensive procedures are indicated, nor do we think that it is necessary to treat the pathways by which pain is referred in order to treat the pain. We are offering a simple explanation for pyorrhea, some cases of face pain, and some unusual and distressing signs of infection and bizarre symptomatology in the region of the face, eyes, ears, and head. We realize that the heyday of pulling teeth as a panacea so discredited the possible relationship between teeth and "disease" (difficult ease) that today this idea is in discard. We ask that this relationship be kept in mind, observing, of course, its proper perspective, especially in those cases where all other possible causes seem to be excluded.

### CONCLUSION

A simple method of diagnosis and treatment of pyorrhea and of some cases of atypical face pain and other bizarre symptomatology is presented.

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## PERIARTERITIS NODOSA—POSSIBLE RELATION TO THE INCREASED USAGE OF SULFONAMIDES \*

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PERIARTERITIS nodosa, formerly considered a rare clinical diagnosis, is now being recognized more frequently. The medical literature of recent years contains many references to this disease. The increase in the number of reports on the subject concomitant with the wide usage of sulfonamides has prompted us to review the records of Bellevue Hospital before and after the availability of sulfa therapy.

Although information regarding the history of drug ingestion in our cases of periarteritis nodosa is lacking, it is generally agreed that such knowledge is difficult to obtain because many patients often receive the drug unknowingly and also that the sulfonamides are being dispensed with great frequency.

There were only four cases diagnosed ante mortem from 1916 to 1937, but from 1938 to 1946 there were 14 cases of periarteritis nodosa detected clinically and proved either by biopsy or necropsy. The latter cases appear below in table 1.

There were nine males and five females whose ages varied from 17 to 63. Eight patients gave a history of bronchial asthma in the past, an incidence of 57 per cent. An eosinophilia of over 10 per cent, ranging from 12 per cent to 41 per cent was present in 43 per cent of the cases. Three patients were discharged as improved, six died and five were unimproved.

The protean manifestations of this disease have frequently baffled the internist. Meyer's original triad of symptoms, i.e., chlorotic marasmus, polyneuritis and polymyositis, and abdominal symptoms, became a tetrad after Brinkman added nephritis to this syndrome. Subsequently additional features were observed so that at present the list of characteristics of this disease has grown. Solomon, Kasich and Kiven<sup>1</sup> separated the clinical and laboratory findings into four convenient groups. First, there are those occurring from the inflammatory process, such as fever, leukocytosis, general malaise, loss of weight, rapid sedimentation rate, anemia, and in general the picture of sepsis of unknown origin. Second, the group of symptoms arising from the involvement of the arteries of particular organs, such as the heart, nervous system, gastrointestinal system and kidneys. Third, the allergic manifestations as evidenced by eosinophilia in the peripheral blood and in the involved arteries histologically as well as the frequent association

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TABLE I

Name	Age	Sex	History of Bronchial Asthma	Biopsy	Autopsy	Eosino- philes	Precipitin Test	X-ray Evidence of Osteopor- osis	Outcome
E. K.	42	M	Yes	Positive	0	1-15	Not done	Not done	Improved
J. F.	54	M	No	Positive	0	3-7	Pos. in 1:1280	Yes	Improved
R. A.	39	F	Yes	Positive	Yes, pos. P.N.	16-18	Not done	No	Died
A. K.	63	M	Yes	Taken from gall-bladder	0	1-3	Not done	No	Discharged
F. W.	59	M	Yes	Positive	0	4	Pos. in 1:1280	Yes	Unimproved
D. B.	47	F	Yes	Positive	0	27-49	Pos. in 1:1280	Positive	Discharged
W. T.	17	M	No	Positive	0	1-5	Not done	Not done	Unimproved
W. B.	52	M	No	Positive	Yes, pos. P.N.	1-7	Not done	Negative	Died
S. D.	29	F	No	Not done	Yes, pos. P.N.	0	Not done	Not done	Died
L. H.	45	F	No	Not done	Yes, pos. P.N.	0	Not done	Not done	Died
B. O.	52	F	Yes	Positive	0	12	Not done	Negative x-rays	Discharged
H. S.	34	M	Yes	Positive	0	35	Negative	Positive x-rays	Unimproved
J. G.	46	M	No	Positive	Yes, pos. P.N.	0	Not done	Negative	Discharged
E. B.	37	M	Yes	Positive	0	15-41	Negative	X-rays not done	Unimproved

TABLE II

Clinical Findings	Laboratory Findings
1. History of bronchial asthma	1. Eosinophilia
2. Cachexia	2. Leukocytosis
3. Polyneuritis and polymyositis	3. Anemia
4. Abdominal symptoms, i.e. (diarrhea, cramps, vomiting)	4. Elevated sedimentation rate
5. Fever	5. Positive precipitin test for trichinosis in a dilution of 1:1280
6. Vascular changes (as seen in eyegrounds)	6. Roentgen evidence of patchy osteoporosis
7. Nephritis and hypertension	7. Positive muscle or skin biopsy
8. Skin manifestations (urticaria, erythema, nodules)	
9. Arthralgia and arthritis	

of asthma; and fourth, palpable arterial nodules and positive muscle or skin biopsy.

Table 2 enumerates the salient features that were recorded in our cases.

It is important to remember that not all the above mentioned criteria must be present in any one case to warrant a clinical consideration of the diagnosis of periarteritis nodosa. However, only a positive biopsy or necropsy can be considered conclusive.

Two features that have not received sufficient notice are worth em-

phasizing. A positive precipitin test for trichinosis in a dilution of over 1:1000 was found in three of our 14 cases. This is significant inasmuch as the test was performed in only five cases. Patchy osteoporosis, as evidenced by roentgen-ray was present in four of our nine patients, which fact can be explained by changes in the vessels supplying the bones.

The pathologic picture of this disease has a characteristic pattern with which most authors agree. According to Arkin,<sup>2</sup> the lesions may be divided into four stages: a degenerative stage, an acute inflammatory stage, a stage of granulation, and a so-called healed stage. The disease involves the smaller and middle sized arteries and arterioles either in segments or in their entirety. The fundamental pathologic change is an inflammatory lesion of the vessel wall with necrosis, fibrinoid alteration and hyalinization of the media of the affected arteries, together with perivascular infiltration with mononuclear and polymorphonuclear leukocytes which are often eosinophiles. Injury of the intima leads to thrombosis and medial injury and dilatation result in the formation of aneurysms, which may rupture and produce fatal hemorrhage. Organization of the thrombosed aneurysms may give rise to firm periarterial nodules.

Many theories have been advanced concerning the etiology of periarteritis nodosa. The very early writers mention syphilis as a possible cause, but with the development of the Wassermann reaction, the idea was no longer tenable. Mechanical causes and parasitic infections were considered as responsible agents but were never proved. Many bacteria and a filtrable virus have been accused but not definitely isolated. Neurologic and toxic factors have had their proponents but with very little support. Hypersensitivity as an etiologic factor in the production of periarteritis was first suggested by Gruber in 1923.<sup>3</sup> Since then many other observers have subscribed to this theory, and the recent work of Rich<sup>4</sup> and Rich and Gregory<sup>5</sup> has added great impetus to this concept. Rich<sup>4</sup> described vascular lesions characteristic of periarteritis nodosa in the viscera of five patients who shortly before death had hypersensitive reactions following therapeutic injections of foreign serum and sulfonamides, and in one patient who had received sulfathiazole prophylactically to prevent aspiration pneumonia. The possibility that the infection for which these patients were treated might be implicated was negated by the experimental reproduction of similar lesions in rabbits by the injection of horse serum and horse serum plus sulfadiazine. These observations caused Rich to advance the idea that periarteritis nodosa may well be a manifestation of hypersensitivity.

## DISCUSSION

We noted the predominance of males over females in a ratio of almost two to one, a fact which is generally well recognized. The frequent association of bronchial asthma with periarteritis nodosa has been observed by many authors. Rackeman and Greene<sup>6</sup> reported an incidence of 12 per cent,

and Wilson and Alexander<sup>7</sup> found a somewhat higher figure, 18 per cent. The 57 per cent that we noted, although considerably higher, can be explained by our relatively small series. The blood eosinophilia of 43 per cent is within the expected range noted by previous writers.

Our series of 14 cases, although not large, is particularly significant in a condition as uncommon as periarteritis nodosa. The significant rise in the number of cases diagnosed after the introduction of sulfonamides suggests the possibility that the drug may play a rôle in the etiology of this disease.

We agree that increased interest in periarteritis nodosa may have been a factor in sharpened diagnostic acumen; nevertheless, the relation of the wider usage of sulfonamides to the figures presented cannot be questioned. In analyzing the necropsy material at Johns Hopkins Hospital, Rich<sup>8</sup> noted that during the years from 1916 to 1935 the characteristic picture of periarteritis nodosa was found in only one or two cases per five year period. In a similar number of autopsies performed from 1936 to 1940 there were 15 cases of periarteritis nodosa and in the five year period from 1941 to 1946 there were 23 cases.

There is sufficient accumulated experimental and clinical evidence to indicate that sulfonamides can produce hypersensitivity. Schönholzer<sup>9</sup> and David<sup>10</sup> demonstrated that sulfa drugs can attach themselves to plasma protein and that the complex so formed can behave as an antigen. Wedum<sup>11</sup> was able to produce anaphylactic shock and positive intradermal reactions by conjugating sulfonamide compounds to human and rabbit serum. Gerber and Gross<sup>12</sup> produced anaphylaxis and the Schwartzman phenomenon in guinea pigs and rabbits with conjugated sulfa compounds. Schaeffer, Lentz and McGuire<sup>13</sup> in 1943, reported a positive Prausnitz-Kustner reaction to sulfathiazole with serum and blister fluid from persons reacting to the drug a second time. Leftwich<sup>14</sup> in 1944 clearly demonstrated that specific cutaneous reactions can occur by employing the serum of patients treated with sulfonamides who gave no reaction, and inoculating it into those who reacted with a typical hypersensitive pattern.

Shortly after sulfonamides were employed clinically, Hageman and Blake<sup>15</sup> in 1937, reported the serum-sickness like reactions of a group of patients who were treated with sulfanilamide. Goodman and Levy<sup>16</sup> were among the first to suggest that the rash appearing after treatment with sulfanilamide was the result of hypersensitivity even though the skin tests in their two cases were negative. Thereafter many similar reactions were noted and reported.

Many observers have described vascular changes resembling periarteritis nodosa following the use of sulfonamides. Lederer and Rosenblatt<sup>17</sup> found necrosis and infiltration of inflammatory cells in the viscera of four patients who died from sulfathiazole intoxication. The histologic picture that Rich<sup>4</sup> noticed in his five cases who received serum and sulfonamides consisted of



fibrinoid necrosis with perivascular infiltration of mononuclear cells and eosinophiles, a picture not unlike that seen in periarteritis nodosa. Although Clark and Kaplan<sup>18</sup> demonstrated a similar arterial lesion in patients who had serum-sickness shortly before death, Rich<sup>19</sup> also observed fibrinoid necrosis at necropsy in two patients who received sulfathiazole without serum. This led Rich to reason that sensitization to sulfonamides does occur and that under such circumstances periarteritis-like lesions may be caused by the administration of the drug.

Rosenak and Maschmeyer<sup>19</sup> reported a case of periarteritis nodosa in a patient who received sulfadiazine and died. More recently, Goodman<sup>20</sup> described a case of periarteritis nodosa proved by biopsy, in whom the apparent cause was sulfadiazine sensitization. The patient recovered following a severe prolonged anaphylactic reaction produced by the unwitting administration of the drug at the height of the patient's illness. Black-Schaeffer<sup>21</sup> in describing five cases of anaphylactic death following therapeutic use of sulfonamides noted arterial lesions which varied from simple edema to frank necrosis. Although the necrotizing vascularitis mentioned was not quantitatively comparable to the typical lesion of periarteritis nodosa, the author felt that the basic pattern was so similar that it suggested a difference of intensity and duration of action rather than the quality of the irritant.

Inasmuch as sulfonamides can produce hypersensitive reactions and a vascular necrosis resembling periarteritis nodosa has been described following its administration, it is reasonable to assume that the increased number of cases of periarteritis nodosa reported clinically at our institution since the introduction of this chemotherapeutic agent may be explained by a hypersensitivity to sulfa compounds.

#### SUMMARY

1. A review of the records of Bellevue Hospital during the years from 1916 to 1937, before the introduction of sulfa therapy, revealed only four cases of periarteritis nodosa diagnosed ante mortem.

2. After the wider usage of sulfonamides, from 1938 to 1946, there were 14 cases recognized clinically and proved either by biopsy or necropsy.

3. A history of bronchial asthma was present in 57 per cent of the cases and eosinophilia of over 10 per cent occurred in 43 per cent of the 14 patients.

4. The pathology and various etiologic factors of periarteritis are discussed.

5. Evidence that hypersensitivity to sulfonamides does exist is presented.

6. The vascular lesions resembling periarteritis nodosa following sulfonamide administration and the increased incidence of periarteritis since the introduction of the drug are offered as evidence that a possible relation exists between sulfonamides and the disease, periarteritis nodosa.

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# OBSTRUCTION OF THE SUPERIOR VENA CAVA: A REVIEW OF THE LITERATURE AND REPORT OF TWO PERSONAL CASES\*

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## INTRODUCTION

THE superior vena caval syndrome is due to obstruction of the superior vena cava, bilateral innominate vein obstruction or arteriovenous fistula between the ascending aorta and superior vena cava. This presentation is limited to a discussion of obstruction of the superior vena cava, either partial or complete. It does not include bilateral innominate vein obstruction or arteriovenous communication between the superior vena cava and ascending aorta, unless these conditions are found coincidentally with superior vena caval obstruction. Perfection of technic of angiography, phlebography, venous pressure, and circulation time has stimulated renewed interest in this syndrome. The clinical picture results from increased venous pressure in that part of the body which normally has its venous return to the superior vena cava, delayed circulation time, collateral diversion of the blood stream, and the associated manifestations of the primary pathologic process causing the obstruction.

## HISTORICAL DATA

There is considerable confusion in the literature in regard to whom credit should be given for priority of publication on this subject. Both Fischer<sup>150</sup> and Ehrlich, Ballou, and Graham<sup>42</sup> state that Corvisart, in 1806, was the first to report marked narrowing of the superior vena cava and Marjolin, in 1819, was the first to report complete obliteration of this vessel. According to Ochsner and Dixon,<sup>89</sup> Zambellini (1900) states that the first two reported cases of superior vena caval thrombosis were by Bartolino and Hunter. In referring to the original publication of Zambellini,<sup>160</sup> we find that he actually gives priority of publication to Bartolino; however, our investigation indicates that Bartolino probably did not publish an authentic case. There are numerous publications by authors named Bartolino or Bartholinus during the 17th and 18th centuries and we find in the writings of Thomas Bartholinus,<sup>148</sup> 1740, reference to a case of death by suffocation in which a post mortem was done by Riolanus, who described a "small bit of flesh with shapeless fat in the orifice of the vena cava." The reference is vague and the author does not state whether the fleshy material was in the inferior or the superior vena cava.

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William Hunter,<sup>151</sup> in "Medical Observations and Inquiries," 1757, reports a case of superior vena caval obstruction from aortic aneurysm in a man who died October 29, 1752. An autopsy was done and drawings were made. On page 333 of his report, in the explanation of the various parts of the first drawing, is the following statement: "L, the vena cava superior; and M, the common trunk of the left subclavian and jugular vein; both so much compressed by the dilated artery as hardly to have anything left of their natural capacity and appearance." This report by Hunter, apparently, is the first authentic description of a case of obstruction of the superior vena cava. Consequently, the literature dates back 190 years and antedates the reports of Corvisart and Marjolin by approximately one-half century.

Following the report by William Hunter,<sup>151</sup> 1752, and later those of Corvisart, 1806, and Marjolin, 1819, came the inaugural dissertations of Deckart, 1823, Weissbrod, 1831, Poschel, 1903, and Fischer,<sup>150</sup> 1904. Fischer's contribution provided the most comprehensive review of the subject up to that time.

#### REVIEW OF THE LITERATURE

Fischer, 1904, collected 252 cases from the literature. In 226 of these, autopsy had been performed. This, according to the author, represented the cases published up to that time "so far as they were available to him." Rauth,<sup>104</sup> however, stated that Hume, in 1903, at the instigation of Osler, reported 29 cases, 12 of which were not included by Fischer. Rauth,<sup>104</sup> 1911, collected nine additional cases from the literature after 1904, all verified by autopsy except one. Dana,<sup>36</sup> 1922, collected 23 more after 1911, and Ehrlich, Ballon, and Graham,<sup>42</sup> 1934, collected eight after 1922. From 1934 to January, 1946, inclusive, we have collected 111 cases, 56 of these proved by autopsy.

We have not searched for reported cases prior to the dissertation by Fischer, 1904, but in the above summaries of the literature from 1904 to 1934 many case reports have been omitted. We have divided the literature arbitrarily into four periods since Fischer's contribution represented by the publications of Rauth,<sup>104</sup> 1904 to 1910, inclusive; Dana,<sup>36</sup> 1911 to 1921, inclusive; Ehrlich, Ballon, and Graham,<sup>42</sup> 1922 to 1933, inclusive; and the portion of our review covering the period 1934 to January, 1946, inclusive. It is assumed that the various authors could not have reviewed the cases published in the year of their own publication with the exception of the cases which they contributed themselves. During the period 1904 to 1933, there are 100 cases in the literature not reported in the summaries of Rauth; Dana; and Ehrlich, Ballon, and Graham; 73 of them proved by autopsy (table 1).

Rauth, in reporting his nine collected cases, did not provide a complete bibliography but mentioned the following authors as source of his material: Osler, Leyden and Westenhoffer, Weinberger, Vigoureux and Collet,

Poeschel, and Revilloid. From this group, we have included only the case of Leyden and Westenhoffer<sup>74</sup> in our series for review. Satisfactory data concerning the cases by Weinberger, and Revilloid could not be obtained. The publications by Osler and Poeschel were in 1903; our review begins with 1904. The case of Vigoureux and Collet apparently was reported in 1905 but had previously been reported by Comby before the Société Médicale

TABLE I  
Case Reports in Literature to 1946

Date	Source		No. of Cases	Bibliographic References		Remarks
				Verified Cases*	Unverified Cases*	
Prior to 1904	Hume, 1903		12			Included for completeness
	Fischer, 1904		252			
1904 to 1910	Rauth	Literature	9			23 of these cases were verified by autopsy
		Personal	4			
	Cases in literature not collected by Rauth		30	2, 13, 26, 32, 38, 41, 50, 56, 63, 65, 66, 69, 73, 78, 91, 105, 106, 108, 119	10, 40, 41, 94, 118, 121, 127	
1911 to 1921	Dana	Literature	23	5, 6, 8, 37, 44, 52, 53, 57, 59, 70, 92, 93, 122, 123, 128, 133, 136, 137, 144, 145	1, 22, 33, 51, 54, 57, 58, 61, 75, 76, 97, 124, 126, 131, 137	Dana's bibliography is incomplete. It is not possible to determine what cases he reviewed. Of the 43 cases in the literature, 25 were verified by autopsy
		Personal	1			
	Cases in literature not collected by Dana		20			
1922 to 1933	Ehrlich, Ballon and Graham	Literature	8	15, 19, 21, 47, 67, 110, 132, 138		Berblinger <sup>15</sup> reported 2 cases; Ehrlich et al. apparently took only one. Of the 50 cases, not reviewed by Ehrlich et al., 25 were verified by autopsy
		Personal	2			
	Cases in literature not collected by Ehrlich, Ballon and Graham		50	15, 27, 34, 62, 72, 84, 86, 87, 88, 100, 113, 114, 116, 117, 120, 129, 140, 141, 142, 147	17, 28, 29, 30, 35, 49, 77, 90, 95, 98, 103, 109, 111, 114, 130, 139, 141, 142, 143, 146	
1934 to Jan. 1946 incl.	McIntire and Sykes	Personal	2			56 of these cases were autopsied
		Literature	111	4, 9, 11, 12, 14, 16, 18, 20, 25, 31, 39, 43, 46, 55, 60, 64, 71, 80, 81, 82, 83, 85, 89, 96, 99, 101, 102, 107, 112, 115, 134, 135	3, 7, 23, 24, 45, 48, 60, 64, 68, 79, 96, 99, 107, 125	
	Total		524			

\* Verified cases—autopsy or surgery done.

.Unverified cases—autopsy or surgery not done.

des Hôpitaux de Paris, January 8, 1892, while the case was under Comby's care. We are not including our two personal cases since this series represents a collection from the literature exclusively. There remains in the total series (table 1) 250 cases from 1904 to January 1946, inclusive, after excluding eight cases by Rauth and our two personal cases. This is an interesting total to compare with Fischer's 252.

Of these 250 cases, the etiology of the obstruction in 145 was proved

by autopsy or surgery. We considered unquestionable proof of etiology dependent upon pathological finding from autopsy or surgery and adhered to this more rigid ruling throughout. The remaining 105 cases were clinical diagnoses, and this group includes only those cases in which there was good evidence in the publications that the patient actually had superior vena caval obstruction.

Doubtless many cases have been missed in the larger series. The report of Hinshaw and Rutledge<sup>60</sup> is a study of 31 cases representing various types of mediastinal obstruction. On the basis of their clinical reports there is sufficient evidence to support the diagnosis of superior vena caval obstruction in only 12 cases. Only four of 50 cases by Pilcher and Overholt<sup>90</sup> are accepted. There are not sufficient diagnostic data available to justify including any of the 30 cases reported by Serra<sup>158, 159</sup> on various types of venous pressure disturbances in mediastinal syndromes. For the same reason, none of 60 cases by Keefer<sup>153</sup> on the subject of acute and chronic mediastinitis are included. None of the 52 cases reported by Hussey<sup>152</sup> are accepted. However, 14 of these had high venous pressure in both arms and it is assumed that they were included in the report of 35 cases by Hussey, Katz, and Yater<sup>64</sup> which are included in our collection.

#### INCIDENCE

In regard to the incidence of the syndrome under consideration, varying opinions are expressed in the literature. Ochsner and Dixon<sup>89</sup> state that "obstructions to the superior vena cava whether partial or complete are rare clinical and pathological entities." Forster<sup>48</sup> states that varying degrees of superior vena caval obstruction occur not uncommonly. We agree with the latter opinion.

It is our feeling that superior vena caval obstruction occurs much more frequently than is generally suspected. Common lesions such as aortic aneurysms, mediastinal malignancies, and chronic inflammatory diseases are responsible for the caval obstruction in a substantial majority of reported cases (table 4). Many cases of superior vena caval obstruction in the literature are doubtless hidden because of being reported as cases of the primary pathology, such as aortic aneurysm, mediastinal lymphoma, etc. Reports of large series of superior mediastinal venous obstruction of various types, such as those of Pilcher and Overholt,<sup>90</sup> Hinshaw and Rutledge,<sup>60</sup> and Serra<sup>158, 159</sup> give additional indication that the disease is not uncommon. It is significant that one group of observers who were alert to this condition, Hussey, Katz, and Yater,<sup>64</sup> should at one time report a total of 35 cases of superior vena caval obstruction, representing nearly 7 per cent of the largest total reported in the world's literature to date, namely our figure of 524 (table 1). The frequency of space occupying lesions of the superior mediastinum, the anatomical relations of the superior vena cava, the easy compressibility of this vessel, and the increasing number of case reports in the

literature (table 1), constitute in our opinion, very suggestive evidence that the syndrome is not uncommon.

### ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The following quotation from Hinshaw and Rutledge<sup>60</sup> is apropos: "The superior mediastinum is the great transportation center of the body. Through it passes all food on its way to the gastrointestinal tract, all air which enters and leaves the lungs, all lymph in the thoracic ducts, all blood which leaves the heart and which returns to it from the superior half of the body. It is surprising that obstructive symptoms do not develop more frequently than they do in this crowded region. It is more surprising still when the frequency with which the numerous mediastinal lymph nodes are involved in tumefactive processes due to inflammatory, tuberculous, and neoplastic lesions is recalled.

"The anterior and posterior boundaries of the superior mediastinum are firm and unyielding parts of the thoracic wall. The lateral boundaries are elastic, being separated from the spongy lungs by nothing more than the pliable pleural layers. Space occupying lesions can thus expand laterally.

"The trachea is well protected by its cartilaginous rings. Although frequently displaced, it is rarely collapsed by extrinsic pressure sufficient to produce obstructive symptoms. The esophagus lies in a somewhat protected region and its elasticity and power of independent motility makes serious functional impairment from extrinsic pressure rather uncommon. The great arterial trunks not only have firm walls, but the contained blood is under pressure sufficient to prevent interruption of the flow by an external force of reasonable intensity.

"The large mediastinal veins on the other hand are thin walled and the blood flowing through them is under very low pressure. Furthermore, these veins are anteriorly situated nearer the unyielding bony thoracic cage, against which they may be compressed by expanding mediastinal lesions. These veins drain blood from the upper half of the body only; from the upper extremities, the head, neck, and thoracic wall. Obstruction to flow of blood in these important channels will produce localized symptoms and signs pathognomonic of a mediastinal lesion. Since these vessels are readily compressed, such manifestations may be early indications (sometimes even initial symptoms) of serious mediastinal disease."

The ascending aorta lies in an anteromedial position to the superior vena cava and is immediately adjacent to it in most of its course (figure 1). Anatomically it seems most unlikely that a large aneurysm of this part of the aorta would fail to compress the superior vena cava to at least a moderate degree. The trachea and right bronchus hold a posterior and close relationship to the vena cava; direct extension to the vein by malignancy involving the anterior part of these structures could conceivably occur without much difficulty.

The importance of the relationship of certain mediastinal lymph nodes to the superior vena cava has not been sufficiently stressed in medical literature dealing with obstruction of this vessel. Two important chains of lymph nodes are intimately associated with the vessel: the right anterior mediastinal and the right latero-tracheal chains (Rouvière<sup>157</sup>). The former lies along the anterior surface of the superior vena cava and the right innominate vein and consists of two to five nodes. The latter lies on the posterior aspect of the same vein and consists of three to six nodes, the

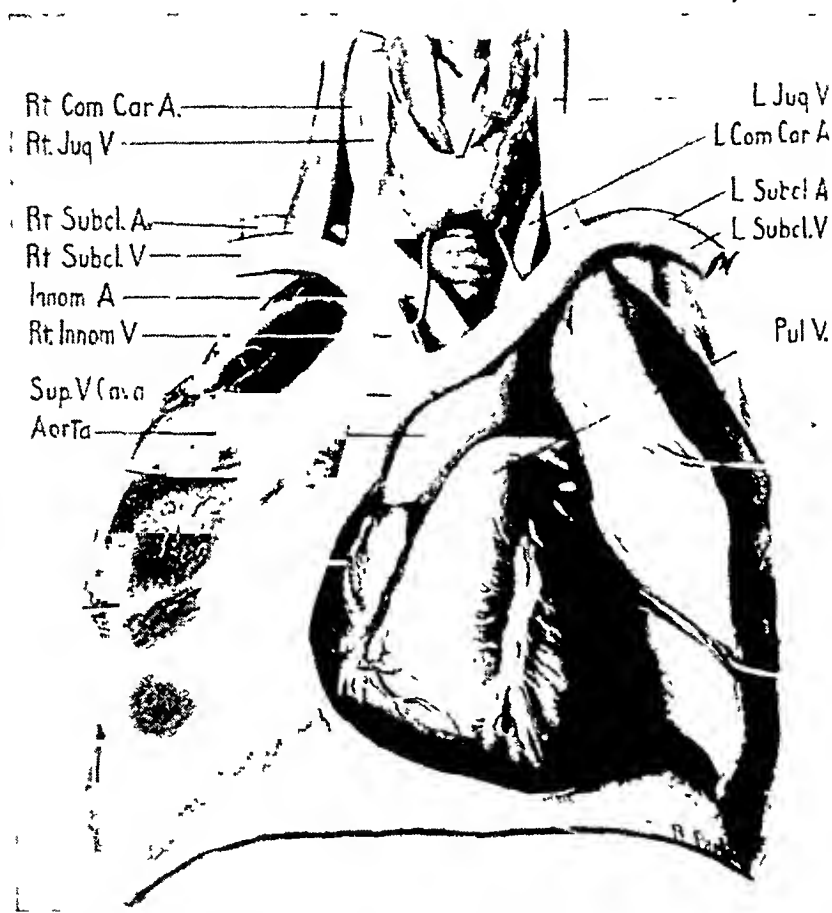


FIG. 1. Anterior view of mediastinal structures, showing the relationship of superior vena cava and ascending aorta. (Figure taken from Hussey.<sup>152</sup>)

largest and most inferior of which lies on the superior surface of the arch of the vena azygos (figure 2). In addition, the right bronchial nodes and some of the nodes of the tracheal bifurcation are in fairly close association with the lower portion of the vena cava; both of these groups of nodes in turn drain into the right latero-tracheal chain. This chain (right latero-tracheal) receives most or all of the lymph drainage from the right lung, the lower trachea and proximal bronchi, the thoracic esophagus, and the lower portion of the left lung (figure 3).



The right anterior mediastinal lymphatic path receives some efferent vessels from the diaphragm, the diaphragmatic and mediastinal pleura, the heart, the pericardium, the right lung, and the thymus.

From the above, it is obvious that most of the structures of the right thoracic cavity, mediastinum, and part of the structures of the left thoracic

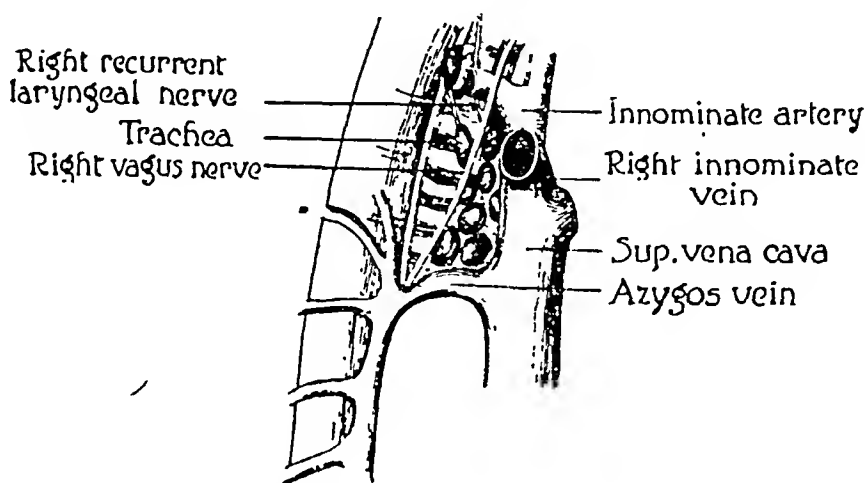


FIG. 2. The right latero-tracheal group of lymph nodes showing relationship between the nodes and the superior vena cava. Nodes are seen in the triangle formed by the azygos arch, the right vagus nerve, and the superior vena cava. (Figure by Sukiennikow, taken from Lerche.<sup>154</sup>)

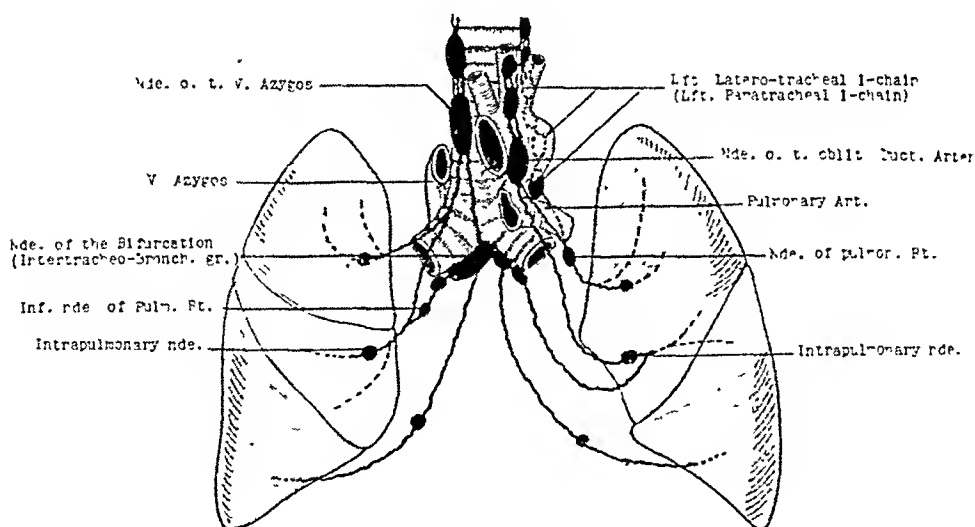


FIG. 3. Schematic representation of the pulmonary lymphatic drainage indicating the great area of pulmonary tissue drained by the right laterotracheal chain (one of the component nodes of this chain is the node of the vena azygos, labeled in this schema). (Figure taken from Rouvière.<sup>157</sup>)

cavity, drain into either or both the right anterior mediastinal and the right laterotracheal chains (figure 3). The frequency of neoplastic and inflammatory disease in this part of the body serves as a constant threat to these lymph nodes with possible obstruction, partial or complete, of the superior vena cava from extrinsic pressure or invasion.

### COLLATERAL CIRCULATION

Collateral diversion of the obstructed venous stream results in one of the characteristic features of the clinical picture—dilatation of certain subcutaneous veins. The efficiency of the collateral circulation is a factor in determining the prognosis and the degree of invalidism associated with the obstruction. Emphasis should be placed therefore upon the collateral routes available to the body. A composite, schematic diagram has been prepared to aid in the understanding of these routes and their mutual relationships (figure 4).

The superior vena caval system possesses four tributaries which carry the main burden of shunting the blood of this system toward the heart around an obstruction. Although none of these tributaries alone affords a direct connection between the superior vena caval system and the heart or inferior vena cava, the name of the tributary primarily involved in a particular route of collateral circulation will be used here to designate the route. Thus the terms internal mammary, vertebral, azygos, and lateral thoracic routes will be used below. All four routes are interconnected and all four are probably concerned in the collateral circulation regardless of whether the obstruction is above, below or involves the vena azygos orifice in the superior vena cava. The level of the obstruction with reference to the azygos orifice will indicate, however, which of the routes will predominate in the collateral flow. It should be realized that the four routes to be discussed do not constitute the total number of collateral pathways available to the body but merely those considered most important. The experimental work of Carlson<sup>149</sup> has been of considerable value in clarifying the subject of collateral circulation in superior vena caval obstruction.

1. *Internal Mammary Route* (heavy stipple—figure 4.) : This route consists of the internal mammary vein, the superior and inferior epigastric, the musculophrenic veins, all the intercostal veins (except those of the first right and upper three or four left intercostal spaces), the anterior and posterior superficial veins of the thorax, the perforating branches of the internal mammary vein, and the medial mammary and posterior rami of the intercostal veins. Into this route is drained part of the blood of the vertebral route. Blood of the internal mammary pathway is ultimately drained into the vena azygos and the external iliac veins.

2. *Vertebral Route* (dark shade—figure 4) : This route is composed of the vertebral and intervertebral veins, and the vertebral plexus (internal and external); it carries blood from the innominate veins and the dural



routes. Its importance and the direction of the blood flow in it vary with the level of the obstruction. When the obstruction is above the azygos orifice the direction of blood flow is normal (toward the superior vena cava) and the vena azygos much dilated, forming an extremely important channel in returning blood to the heart (Carlson). When the obstruction involves the azygos orifice the blood flow is apparently reversed and the vena azygos diminished in size, forming a relatively unimportant collateral pathway (Carlson<sup>140</sup>). The part played by the azygos route when the obstruction is placed below the azygos orifice has not been determined experimentally; the two dogs Carlson subjected to superior vena caval ligation in this location failed to survive long enough for the collateral circulation to be studied. Presumably, however, the flow is reversed in this case, and theoretically the azygos route should form an important link connecting the superior vena caval system with the inferior vena cava.

4. *Lateral Thoracic Route* (light stippling—figure 4): This route consists of the lateral thoracic, thoraco-epigastric, superficial epigastric, and superficial circumflex iliac veins, their contained blood being poured into the femoral vein via the long saphenous vein. Being superficial, the veins of this route are readily seen when in a dilated state and are, therefore, of clinical importance. When the dilatation results from an obstructed superior vena cava the direction of blood flow is downward. Between this collateral pathway and the internal mammary route there exist communications which Carlson found to be extensively developed in the dog when the obstruction involved the azygos orifice. Only in obstructions at this level did the above author find the lateral thoracic route to be well developed; it was relatively unimportant where the obstruction was located above the azygos orifice.

## ETIOLOGY

As indicated, our study is based on a series of 250 published cases appearing in the literature since 1904. In 166 of these the sex is given, 79.5 per cent being males and 20.5 per cent females. In Fischer's<sup>150</sup> series, 71.3 per cent were males and 28.6 per cent females. Thirty of the 35 cases reported by Hussey, Katz, and Yater<sup>64</sup> were males. These authors<sup>64</sup> explain the sex incidence on the basis of preponderance of aneurysms, bronchogenic carcinoma, and malignant lymphoma in the male.

Age was given in 164 cases in our collection and in 220 of Fischer's. We have shown the incidence in each decade of life in both series, as well as combined totals. The highest incidence is from age 30 to 60, probably corresponding to the age incidence of the common etiological factors, more particularly neoplasms and late syphilis, including aortic aneurysms (table 2).

We have not included, in our series, cases of mediastinal emphysema and pericardial obliteration as etiologic factors. For the sake of simplicity we have included, under the heading malignant lymphoma, cases listed in the

literature as lymphoma, lymphocytoma, lympho-adenoma, lymphosarcoma, lymphoblastoma, malignant lymphogranuloma, and Hodgkin's disease.

There is an attempt in some of the case reports to differentiate between tuberculous lymphadenitis and mediastinitis. A similar attempt is made to differentiate between gummatous and non-gummatous syphilitic mediastinitis. The differentiation of these two types of tuberculosis, as well as the two types of syphilis, lends itself to considerable inaccuracy, particularly when it is made on the basis of case histories, and probably is largely of academic interest. Consequently, we have grouped our cases of tuberculous lymphadenitis and mediastinitis together into one heading of tuberculosis and our cases of gummatous and non-gummatous syphilitic lesions under one heading of syphilis (table 3, Group V, A and B).

TABLE II

Age Period	No. Cases 1904 to Jan. 1946, Inc.	No. Cases before 1904 (Fischer)	No. Cases— Both Series	Per Cent— Both Series
0-10	1	3	4	1.04
11-20	9	12	21	5.48
21-30	24	33	57	14.85
31-40	33	38	71	18.50
41-50	38	71	109	28.40
51-60	36	33	69	17.95
61-70	18	27	45	11.70
71-80	3	3	6	1.56
81-90	1	0	1	0.26
91-100	1	0	1	0.26
Totals	164	220	384	100.00%

In tabulating etiology and disease incidence in the authors' collected series, the general plan of Ehrlich, Ballou, and Graham<sup>42</sup> in classifying Fisher's<sup>150</sup> cases has been followed. Comparative figures of disease incidence for both series are provided as well as the combined total. Percentage figures for Fischer's series are taken from Ehrlich, Ballou, and Graham.<sup>42</sup> Bibliographic references are listed according to etiology and separated into verified and unverified groups (table 3).

It is apparent that malignant primary thoracic tumors, aneurysms, and chronic fibrous mediastinitis are responsible for the obstruction in 75 per cent to 80 per cent of the cases in both Fischer's and the authors' series (table 4). Primary thoracic tumors, benign and malignant, account for 35.9 per cent of the cases in the combined series. Approximately 93 per cent of these are malignant. Syphilis (mediastinitis and aortic aneurysm) accounts for 34.8 per cent of the cases in the authors' collected series. Approximately 69 per cent of these are aortic aneurysms. Fischer's series was not included in this group since the subject of syphilitic mediastinitis, in his report, is rather obscure.

TABLE III  
Etiology of Superior Vena Caval Obstruction

Group	Etiological Factor	Bibliographical Reference		Authors' Series				Fisher's Series (1)	Combined Series 2)
		Verified Cases*	Unverified Cases*	V*	U*	Total	%		
I.	Propagating thrombi from periphery	38, 101	23, 97	2	2	4	1.6	4.0%	2.8%
II.	Localized phlebitis with thrombus formation	12, 14, 16, 20, 25, 31, 32, 44, 73, 83, 115, 116, 117, 134	61, 96, 125	16	3	19	7.6	1.5%	4.55%
III.	Tuberculous phlebitis			0	0	0	0	1.5%	.75%
IV.	Actinomycosis			0	0	0	0	.5%	.25%
V.	Traction or compression by scar tissue (chr. mediastinitis)			30	32	62	24.8	6.0%	15.4%
	X A. Tuberculous	18, 55, 60, 66, 73, 78, 88, 92, 119, 135, 140	17, 48, 54, 99, 114, 126, 131	11	8	19			
	X B. Syphilitic	13, 15, 34, 37, 44, 91, 110, 129	11, 22, 33, 40, 51, 54, 75, 76, 94, 95, 98, 99, 103, 146	12	15	27			
	X C. Unknown—"idiopathic"	43, 55, 89, 112, 132	45, 49, 60, 96, 142	7	9	16			
VI.	Obliteration of pericardium			0	0	0	0	.5%	.25%
VII.	Thoracic tumors								
	A. Primary thoracic tumors								
	1. Benign	56, 81	79	2	1	3	1.2	4.0%	2.6%
	2. Malignant			48	26	74	29.6	37.0%	33.3%
	X a. Lung and bronchi	6, 21, 36, 39, 46, 64, 67, 80, 82, 102, 104, 136, 137, 142	60, 64, 107	19	3	22			
	X b. Esophagus	136		1	0	1			
	X c. Thymus	2, 19, 47, 122, 133		5	0	5			

TABLE III—Continued

Group	Etiological Factor	Bibliographical Reference		Authors' Series			Fischer's Series (1)	Combined Series (2)
		Verified Cases*	Unverified Cases*	V*	U*	Total		
	X d. Malignant lymphoma	8, 42, 53, 64, 72, 96, 99, 147	3, 24, 35, 45, 60, 96, 99, 107, 137, 141, 142	12	17	29		
	X e. Chorionepithelioma	46		1	0	1		
	X f. Leukemia	52, 64		3	0	3		
	X g. Sarcoma	57, 60, 107, 137, 142	57, 130	5	2	7		
	X h. Unclassified	72, 114	1, 121, 141, 142	2	4	6		
	3. Unclassified	106, 113	7, 57, 64, 114, 127	2	10	12	4.8	2.4%
	B. Extrathoracic malignant tumors							
	1. Metastasis to thoracic organs	42, 64, 142	3	4	1	5	2.0	3.125%
	2. Tumors breaking into tributary of S.V.C. and growing down into it			0	0	0	0	2.125%
	3. Metastasis to vein wall itself			0	0	0	.5%	.25%
	C. Aortic aneurysm			39	21	60	24.0	30.0%
	1. Aneurysm alone	9, 41, 50, 62, 64, 84, 100, 102, 104, 123, 128, 129, 138, 141, 144	3, 28, 29, 30, 41, 45, 64, 90, 109, 111, 124, 139	18	21	39		
	X 2. Aneurysm with perforation into S.V.C.	4, 5, 10, 26, 27, 59, 63, 64, 65, 66, 69, 70, 71, 74, 85, 93, 105, 108, 120, 145		21	0	21		
VIII.	X Etiology not stated	86, 87	58, 64, 68, 77, 118, 143	2	9	11	4.4	2.2%
			Total	145	105	250	100	100%

\* "V"—Verified cases—autopsy or surgery done.

"U"—Unverified cases—autopsy or surgery not done.

(1) Fischer's series—252 cases.

(2) Combined series—502 cases.

X Additions to Ehrlich, Ballon and Graham's table.

There are 74 malignant primary thoracic tumors in our collection, 48 of which were proved by autopsy (table 5). Twenty-five per cent of these verified cases are due to malignant lymphomas of various types; and approximately 40 per cent are due to malignancy of lung and bronchi, all reported as carcinomas except two, which are stated to be primary fibrosarcoma of the bronchi.<sup>137, 142</sup> Figures based on unverified cases are not reliable (table 5).

TABLE IV  
Percentage Table—Major Etiologic Groups (See Table 3)

Etiological Group	Authors' Series			Fischer's Series	Combined Series (502 Cases)
	Total Series— Verified by Autopsy (145 Cases)	Total Series— Not Verified by Autopsy (105 Cases)	Total Series— Verified and Unverified (250 Cases)	252 Cases— 226 with Autopsy	
Traction or compression by scar tissue (chronic mediastinitis)	20.7	30.5	24.8	6	15.4
Primary thoracic tumors —malignant	33.0	24.7	29.6	37	33.3
Aortic aneurysms	26.9	20.0	24.0	36	30.0
Total	80.6%	75.2%	78.4%	79%	78.7%

Aneurysms have been subdivided into aneurysms alone and aneurysms with perforation into the superior vena cava, or arteriovenous aneurysms. Hussey, Katz, and Yater,<sup>64</sup> in referring to previous reviews of Fischer,<sup>150</sup> Brown,<sup>21</sup> and Ehrlich, Ballou, and Graham,<sup>42</sup> state that the only etiological factor not included in the reviews above mentioned is communication between an aortic aneurysm and the superior vena cava. Our findings are at variance with those of Hussey, Katz, and Yater.<sup>64</sup> In referring to Fischer's publication, we find the report by Pepper and Griffith<sup>155</sup> in his bibliography and note that Fischer included at least 15 of Pepper and Griffith's 29 cases in his report. The case by Leyden and Westenhoffer,<sup>74</sup> reported by Rauth,<sup>104</sup> is one of arteriovenous aneurysm. Hussey, Katz, and Yater have two cases of aortic aneurysm with arteriovenous fistula in their publication. We have included case reports of this type in our collection provided there was stated to be a definite associated occlusion or constriction of the superior vena cava. There are 21 of these cases in our total, all of them proved by postmortem examination. The subject of arteriovenous aneurysm involving the aorta and superior vena cava has been admirably reviewed by Pepper and Griffith<sup>155</sup>; Shennan<sup>120</sup>; and Armstrong, Coggin, and Hendrickson.<sup>4</sup>

Nineteen cases of localized phlebitis with thrombus formation have been reported since 1904, 16 of them verified by autopsies. In regard to etiology, 11 were of unknown cause, three were associated with cardiac disease, three were caused by mediastinitis, one was associated with silicosis, and one was classified as tuberculous endophlebitis. Fischer has a group of tuberculous



endophlebitis cases, listed by Ehrlich, Ballou, and Graham as comprising 1.5 per cent of his series. However, it is our opinion that these cases should be placed in the group "Localized Phlebitis with Thrombus Formation." Consequently, our one case is placed in that category.

TABLE V  
Percentage Table—Primary Thoracic Tumors, Malignant—(See Table 3)

Etiological Factor	Verified by Autopsy (48 Cases)	Not Verified by Autopsy (26 Cases)	Combined Groups—Verified and Unverified (74 Cases)
Malignancy of lungs and/or bronchi	39.60	11.5	29.70
Malignancy of esophagus	2.09	0	1.35
Malignancy of thymus	10.40	0	6.75
Malignant lymphoma	25.00	65.5	39.20
Chorionepithelioma	2.09	0	1.35
Leukemia	6.25	0	4.07
Sarcoma	10.40	7.7	9.45
Unclassified	4.17	15.3	8.13
Total	100%	100%	100%

The "Traction or Compression by Scar Tissue" group has been divided into three subheadings: tuberculosis, syphilis, and a group of unknown cause. This, we believe, follows the intent of Fischer who mentions tuberculosis and syphilis as causative agents as well as a group of cases known as "indurated mediastinopericarditis." Terminology is simplified and clarified by referring to this group as one of chronic fibrous mediastinitis of tuber-

TABLE VI  
Percentage Table—Chronic Fibrous Mediastinitis Group (See Table 3)

Etiological Factor	Verified by Autopsy (30 Cases)	Not Verified by Autopsy (32 Cases)	Combined Series—Verified and Unverified (62 Cases)
Tuberculosis	36.7	25.0	30.7
Syphilis	40.0	47.0	43.5
Fibrous mediastinitis, "idiopathic"	23.3	28.0	25.8
Total	100%	100%	100%

culous, syphilitic or idiopathic origin. Since 1904 a total of 62 cases have been reported and the incidence of each of the etiologic factors is shown in table 6. Change in the incidence of these factors is represented in table 7 according to time intervals corresponding to the reports of Rauth; Dana, Ehrlich, Ballou, and Graham; and the interval which we are reporting. The spectacular drop in incidence of chronic syphilitic mediastinitis from 28.6 per cent down to 0.9 per cent speaks well for the improvement in modern

diagnostic technic and the efficacy of present antisyphilitic therapy. The gradual decline in the incidence of chronic tuberculous mediastinitis from 11.4 per cent to 5.4 per cent is not as spectacular, but nevertheless speaks well for the effectiveness of modern measures in the prevention and treatment of tuberculosis. Idiopathic, or non-specific, chronic fibrous mediastinitis has only recently been reported as such, the first cases appearing in the literature in the period 1922 to 1933. During that interval the incidence was 5.0 per cent. This increased to 11.7 per cent in the 1934 to 1946 period.

TABLE VII

Percentage Change in Incidence (1904-1946)—Chronic Fibrous Mediastinitis Group

Time Interval	1904-1911, Incl.	1911-1921, Incl.	1922-1933, Incl.	1934-Jan. 1946, Incl.
Total case reports—Vena caval obstruction	35*	44	60	111
Tuberculous mediastinitis	11.4% (4 cases)	9.1% (4 cases)	8.3% (5 cases)	5.4% (6 cases)
Syphilitic mediastinitis	28.6% (10 cases)	18.2% (8 cases)	13.3% (8 cases)	0.9% (1 case)
Chronic fibrous mediastinitis— "idiopathic"	0	0	5.0% (3 cases)	11.7% (13 cases)

\* 8 cases by Rauth not included.

In the early case reports of chronic fibrous mediastinitis (traction or compression by scar tissue), particularly those included in Fischer's series, there is room for considerable diagnostic error, especially in unautopsied cases. The diagnostic measures, so important in differentiating the etiological factors in this group, were not available until the latter part of the 19th century or the first part of the 20th century. Koch announced the isolation of the tubercle bacillus in 1882. Roentgen announced his discovery of the value of the roentgen-ray for diagnostic purposes in 1896, and Wassermann described his complement fixation test for syphilis in 1906. Consequently, it is not peculiar that Fischer's series contained only 6 per cent resulting from traction or compression by scar tissue whereas our series contains 24.8 per cent (table 4).

Chronic fibrous mediastinitis of idiopathic, or non-specific, origin is deserving of detailed consideration. In regard to this group, Erganian and Wade<sup>43</sup> reached the following conclusions: "(1) Occlusion of the superior vena cava is, in a small percentage of instances, due to an anatomic entity designated as chronic fibrous mediastinitis. (2) The gross and microscopic features of the condition are characteristic: a poorly defined mass in the superior mediastinum composed of dense collagenous tissue with foci of infiltration with leukocytes and calcification. (3) Etiologic factors are indefinite, but it seems likely that a mild inflammation of the mediastinum

in an individual with tendency to excessive cicatrization may slowly progress to form the typical dense mass of fibrous tissue."

For the development of the scar tissue there must be some antecedent etiological factor such as upper respiratory infection, influenza, bronchopneumonia, tularemia, trauma, rheumatic fever, plus occasionally a tendency to the development of excessive amounts of cicatricial tissue. We have carefully reviewed this group, taking into consideration possible etiological factors and the time relationship between these factors and the subsequent development of obstruction of the superior vena cava. Histories, in a high percentage of reported cases, reveal an antecedent infection of the respiratory tract, or trauma. The respiratory infection may have occurred months or years before symptoms of obstruction appeared.

Case 1, by Erganian and Wade,<sup>43</sup> developed symptoms five years after skinning some rabbits. At the time of the original infection he showed many of the clinical features of tularemia. Case 2, by the same authors, showed evidence of unusual tendency toward scar tissue formation, as shown by a keloid of a midline abdominal scar. Case 3, by the same authors, showed evidence of vena caval obstruction, beginning one year after a severe respiratory infection with bloody sputum and pleurisy.

Detailed histories are not given by Hinshaw and Rutledge<sup>60</sup>; consequently, the possible etiological factors cannot be reviewed in their cases.

Ochsner and Dixon<sup>89</sup> report a case probably resulting from trauma. There is likewise a history of trauma in case 1, by Gray and Skinner,<sup>55</sup> the injury occurring 10 months prior to the onset of symptoms.

Case 2, by Gray and Skinner,<sup>55</sup> gives a history of several attacks of pneumonia prior to 11 years of age. The patient was 27 at the time of the report. Fibrous tissue and a lymph gland removed at the time of surgery for pathological study showed only chronic inflammatory change.

Strausz<sup>132</sup> reported mediastinal fibrosis 10 years after influenza in a patient 24 years of age.

In our case 1 of chronic fibrous mediastinitis, a female aged 27, the history dates back to five years of age, at which time the patient had bronchopneumonia. Two years later she developed symptoms which apparently were quite characteristic of beginning superior vena caval obstruction.

Lerche<sup>154</sup> has pointed out that mediastinal lymph nodes often become infected as a result of infection of the respiratory tract and preëminently so the tracheo-bronchial groups. He furthermore indicates that in whatever way the microorganisms enter the lungs, they ordinarily are carried off from the lungs and bronchi by the lymphatics of the tracheobronchial lymph nodes. These nodes may serve as important germ harboring depots. Microorganisms may be present in them without other demonstrable foci in the body. Lerche's case 1 seems significant in regard to time interval in which these bronchial nodes may serve as germ harboring depots before suppuration. The patient was a farmer, age 46, who gave a history of a

severe attack of influenza at age 39. Following this illness, he had a persistent, dry, hacking cough. About three months prior to consultation he noted pain in the upper part of the chest, behind the sternum and to the right. After due study a diagnosis of mediastinal abscess due to suppuration of the right tracheobronchial group of lymph nodes was made. Shortly thereafter the abscess ruptured spontaneously into the trachea. Cultures of the pus showed pneumococci predominating. Fibrosis with or without actual suppuration must develop from such a process, and eventually produce vena caval obstruction if properly located. (A sterile abscess was found in our case 1 at the time of surgery.)

The striking uniformity in these histories concerning previous severe respiratory infection or thoracic trauma indicates strong probability that the infection or trauma bears a causal relationship to the subsequent development of "idiopathic," or non-specific, chronic fibrous mediastinitis and eventually superior vena caval obstruction. In view of the probable etiological importance of acute respiratory tract infection and in view of the present effectiveness and availability of sulfonamide and antibiotic therapy, it is reasonable to expect a drop in incidence of this type of mediastinitis in future statistics.

### SYMPTOMATOLOGY AND CLINICAL FINDINGS

The symptomatology and clinical findings of the syndrome under consideration, except for the primary pathology involved, is secondary to obstruction of circulation in the superior vena cava. This obstruction causes increased venous pressure in that part of the body which normally has its venous return to the superior vena cava, and collateral diversion of the blood stream. There may or may not be delay in circulation time. As a result of this obstruction and the coincidental change in venous pressure, dilated veins are often visible in the upper half of the body, and edema in the upper extremities, head and neck is frequently noted. Often cyanosis and dyspnea are present. Headache and chest pain are commonly troublesome. Other signs and symptoms which are sometimes associated with this syndrome are hoarseness, dysphagia, drowsiness, and occasionally convulsions. The above clinical findings in the presence of elevated venous pressure in the upper extremities, and normal venous pressure in the lower extremities are sufficient to make a diagnosis of superior vena caval syndrome. Further proof can be obtained by diodrast visualization according to the technic of Robb and Steinberg.<sup>107</sup>

### TREATMENT

Treatment of this condition is largely a matter of treating the primary disease. Symptomatic relief may be afforded by repeated phlebotomies; surgical intervention in selected cases may be justified in an attempt to relieve the obstruction, if due to external pressure. The experience of Gray and

Skinner<sup>55</sup> indicates that mediastinotomy with release of constrictive bands is indicated in those cases of superior vena caval obstruction from chronic mediastinitis in which the venous pressure is increasing and in which the symptoms are progressing.

### PROGNOSIS

Prognosis is largely the prognosis of the primary disease. Since malignancy and aneurysm are the etiological factors in over 70 per cent of the cases, prognosis naturally is rather poor. Cases in which the etiological factors carry a favorable prognosis may live for years in relative comfort after adequate collateral circulation has been established. This was admirably shown in the cases of Blasingame,<sup>16</sup> Fitcher,<sup>51</sup> Meixner,<sup>86, 87</sup> and Mann.<sup>77</sup> The case of Blasingame was 93 years of age, having complete obstruction of the superior vena cava and extensive collateral circulation proved by anatomical dissection. (The anatomical specimen is on display in the Museum of the Department of Anatomy, at the University of Texas School of Medicine at Galveston.)

Our case 1 apparently has had symptoms from vena caval involvement since seven years of age and has developed extensive collateral circulation as proved by surgery and diodrast visualization; however, during much of the time since the onset of symptoms, the patient has been incapacitated.

### CASE REPORTS

*Case 1.* A female practical nurse, age 27, was admitted to the St. John's Hospital on February 8, 1939 for treatment of an acute respiratory infection, which subsided satisfactorily in six days under conservative therapy.

*Past History:* History was obtained of frequent respiratory infections after the age of five. At five years of age, she had a severe case of bronchopneumonia. Condition at the time was critical and she experienced a prolonged convalescence. Two years later she developed dyspnea of unusual intensity, which she described as asthmatic breathing, during physical exercise. At 14 years of age, a throbbing sensation developed in her head. The troublesome dyspnea on physical exertion continued. At 19 years of age, she first noted swelling of the face and neck, chest pain, and nose bleed. Dyspnea on exertion, head throbbing and pain (especially with the head lowered), chest pain and cough, recurring edema of face, neck, and upper extremities, have been troublesome to date. Her history, otherwise, was irrelevant.

*Physical Examination:* Patient was well developed and nourished, acutely dyspneic, respirations shallow, skin moderately cyanotic, coughed frequently, and complained of acute substernal discomfort. The external jugular, median basilic, and cephalic veins were unusually prominent, especially on the left side. Her blood pressure was 110 mm. of mercury systolic and 70 mm. diastolic in the arms and 125/85 in the legs. Temperature was 101.2°, pulse 110, respirations 28. The heart was normal, except for moderate tachycardia. There were a few basal râles in the left chest posteriorly and suppressed breath sounds over the entire lung field. Physical examination otherwise normal. Clinical impression was acute respiratory infection with probable mediastinal tumor.

*Laboratory Studies:* Hemoglobin 90 per cent; red blood cells 4,420,000; white cells 14,000; 85 per cent polys; 15 per cent lymphocytes; Wassermann test negative.

Roentgen-ray studies showed moderate infiltration at the base of the left lung. In the superior mediastinal space a shadow was noted which extended to the right. Radiological diagnosis was probable mediastinal tumor and early bronchopneumonia left base. She was discharged from the hospital February 14 apparently recovered from the acute respiratory infection.

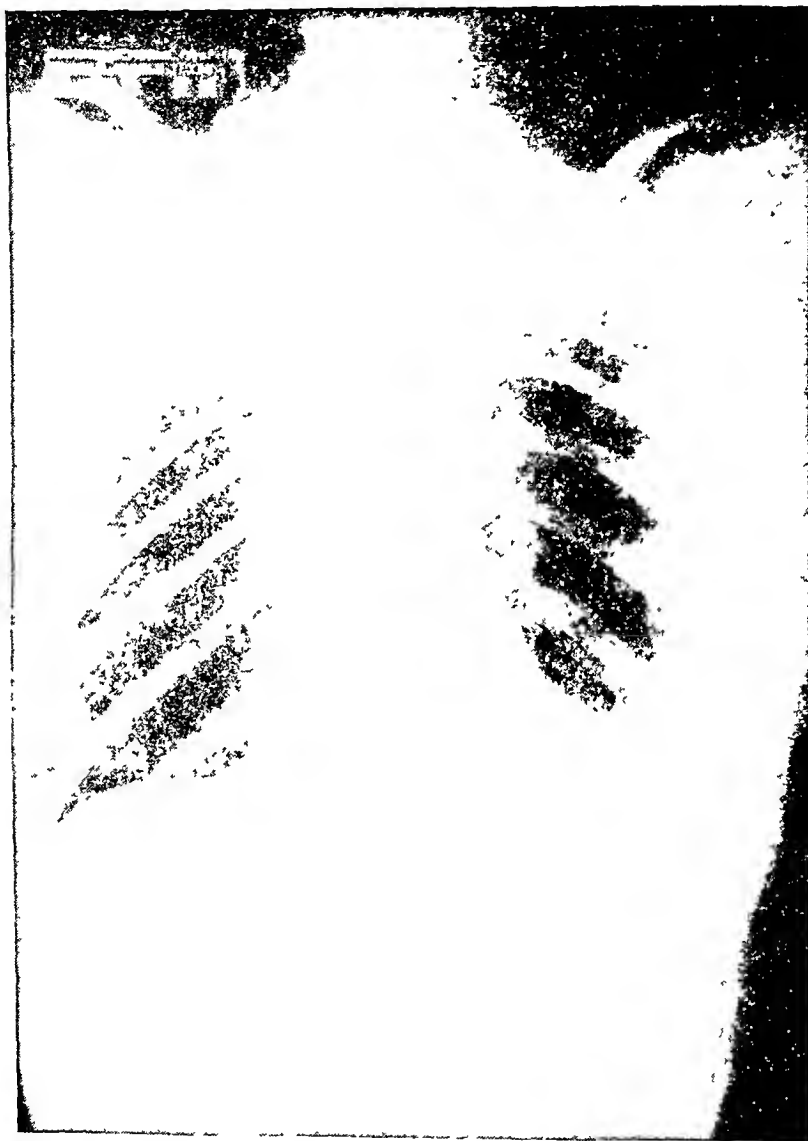


FIG. 5. Chest roentgenogram, February 11, 1939, showing abnormal shadow in right mediastinum. Inflammatory change left base.

On March 9, 1939, she was admitted to the Shannon Memorial Hospital for additional diagnostic studies. Roentgen-ray studies of the esophagus and bronchoscopic examination were both normal. During this admission, a therapeutic trial of radiation was given. This was repeated April 22. No change in the size of the mediastinal tumor was noted following roentgen-ray therapy. Symptomatic change was indefinite.

She was re-admitted to the Shannon Hospital in March of 1940 for treatment of an acute upper respiratory infection, which promptly subsided.

The patient's symptoms of dyspnea, cough, thoracic pain, and headache had persisted. Prominence of the superficial veins and recurring episodes of edema in the upper portion of the body had continued. Cyanosis was prominent. These clinical findings, a persistent mediastinal tumor by roentgenogram, lack of response to radiation, and normal bronchoscopic studies, made it imperative that further investi-



FIG. 6. Diodrast studies, June 20, 1941, showing obstruction of superior vena cava with extensive collateral circulation.

gation be conducted. Consequently, intravenous diodrast studies, according to the technic of Robb and Steinberg<sup>107</sup> were made June 20, 1941. The circulation time, arm to tongue, was 20 seconds. The diodrast studies demonstrated obstruction of the superior vena cava with a large tortuous azygos vein and prominent mammary veins (figure 6). In view of these findings, it was felt that exploratory surgery was indicated, and arrangements were made with Dr. Claude Beck, of Cleveland, for this work.

The patient was admitted to the Lakeside Hospital, Cleveland, April 1, 1942. Her history and physical findings were essentially the same as given above. The hemoglobin was 75 per cent; and the red cells 4,420,000; white cells 7,000; Kline exclusion test negative; vital capacity 3100 c.c.; venous pressure in the right arm, 20 cm.; left arm, 17½ cm.; the left leg was 7.5 cm.; circulation time, arm to tongue, 20 seconds; blood urea nitrogen, 8.3 milligrams per 100 c.c.; urea clearances were normal; intradermal tuberculin test was positive in 48 hours. Roentgenographic studies of the chest showed a rounded mass to the right of the mediastinum opposite the aortic arch, 5 cm. long and 1 to 2 cm. in width. It was located anteriorly in the chest but did not displace the trachea. It did not pulsate. Tentative diagnosis was obstruction of the trachea and superior vena cava, due either to malignant neoplasm or an inflammatory mass.

On the eleventh hospital day, a mediastinal exploration was performed by Dr. Beck. A dense inflammatory mass was found to encircle the superior vena cava and trachea. This was largely removed. At the carina, a small abscess was encountered containing 5 to 10 c.c. of pus. This was evacuated. Powdered sulfathiazole was placed in the cavity. At the end of the operation, the surgeon felt that there was no obstruction to the vena cava and the trachea seemed to be considerably freer.

Her postoperative course was satisfactory until the thirteenth day when she developed pain and tenderness along the course of the right axillary and brachial veins. The following morning she experienced a sudden episode of pain in the chest with dyspnea and cyanosis, rapid pulse and drop in blood pressure. This was believed to be the result of pulmonary embolism originating from the right axillary vein. Continuous heparinization was started and the right subclavian vein was ligated. A few days following the ligation the venous pressure readings were 30 cm. in the right arm and 16 cm. in the left. She gradually improved and was up walking around the ward without much discomfort at the time of her discharge on the forty-eighth hospital day, apparently showing progressive subjective improvement.

Provisional diagnosis was: (1) partial tracheal obstruction due to scar; (2) obstruction of superior vena cava due to scar; (3) sterile abscess of infratracheal lymph nodes.

*Pathological Report:* Guinea pig injection of pus aspirated from the thoracic abscess was negative for tuberculosis. Histological examination of the tissue removed at the time of surgery showed the following findings as reported by T. C. Laittly, M.D. "Representative sections of the specimen show it to be composed of dense collagenous connective tissue. Throughout, there is evidence of fibrosis and there is considerable infiltration with inflammatory cells, the majority of which are lymphocytes. There are also scattered large round cells, and there are irregular pink fibers that contain granular blue material resembling calcium. There is no tubercle formation, or evidence of malignant tumor in the sections examined.

"Section stains by the Von Kossa method show identifiable calcium in the tissues. Section stains by the Masson-trichrome method identify most of the tissue as collagenous connective tissue of adult type. Section stains by the Ziehl-Neelsen technic show no identifiable tubercle bacilli. Histologic diagnosis is chronic inflammation of fibrous connective tissue with focal calcification and heteroplastic bone formation (mediastinum)."

*Follow-up Note:* After returning to San Angelo the patient remained symptomatically improved for approximately one year and then gradually developed a return of her previous symptoms of headache, chest pain, nausea and vomiting. The severity of her symptoms gradually increased until they were about the same as before surgery.

In February, 1946, diodrast studies were repeated, according to the Robb and Steinberg<sup>107</sup> technic and showed changes essentially the same as those seen at the first visualization before surgery, the superior vena cava being completely obstructed



(figure 8). Circulation time, arm to tongue, was 20 seconds. The venous pressure reading, left arm, was 35 cm.

In an attempt to relieve headache, a spinal puncture was done. Spinal fluid pressure was 250 mm. of water; 15 c.c. of clear colorless fluid were removed after which the spinal fluid pressure was 150 mm. This gave the patient no relief, in fact, seemed to aggravate her headache. Temporary partial relief was obtained from phlebotomy. Recent bronchoscopic and esophagoscopy examinations showed no

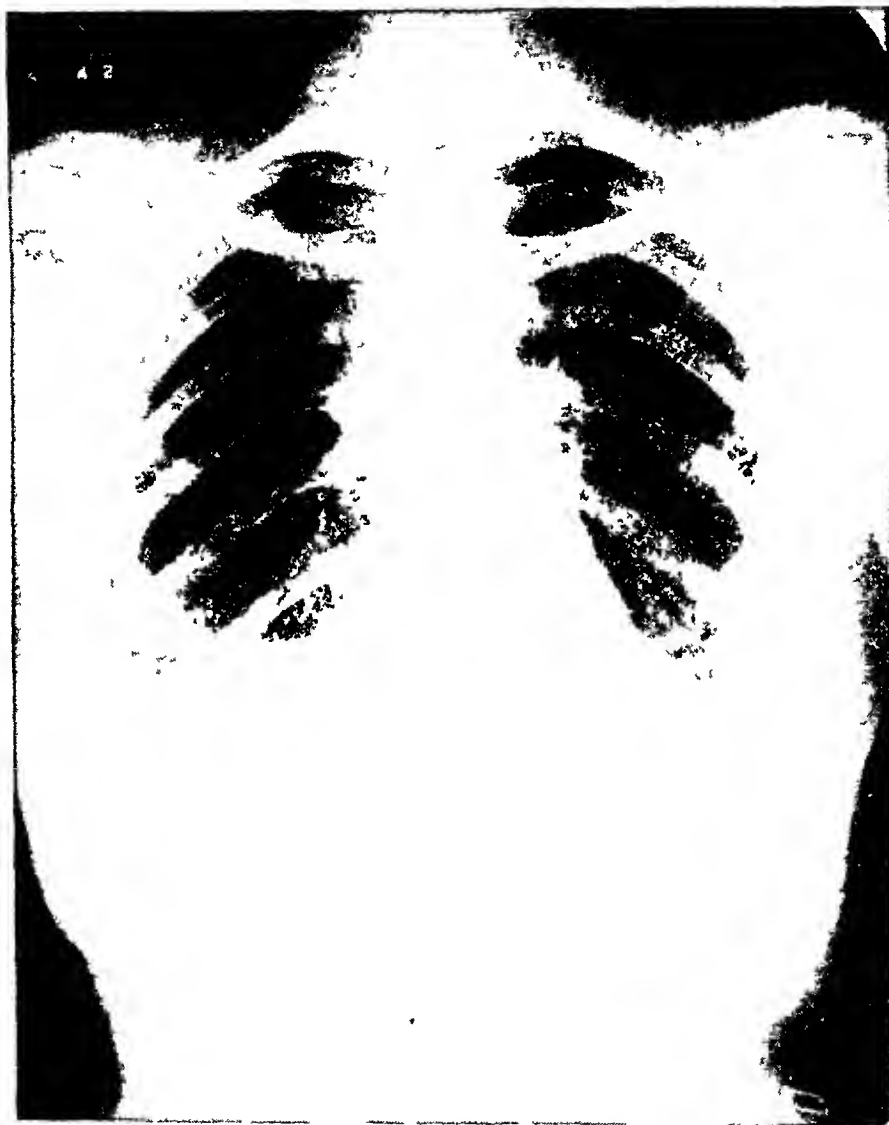


FIG. 7. Postoperative roentgenogram, July 6, 1942, showing reduction in size of mediastinal mass (see figure 5).

evidence of obstruction. She remains on symptomatic measures. Her symptoms are increasingly more difficult to control. Additional surgery has been considered. However, in view of the absence of esophageal and bronchial obstruction, the presence of complete obstruction of the superior vena cava, and the excellent collateral circulation as demonstrated by recent diodrast studies, additional surgery is probably contraindicated. The present venous return seems quite adequate (figures 8, 9 and 10).

This patient apparently is a case of chronic fibrous mediastinitis as described by Erganian and Wade. She demonstrates evidence of gradual obstruction of the superior vena cava over a long period of time, apparently a result of severe respiratory infection in childhood with frequent repeated insults of similar nature since the original episode. This prolonged time interval bears considerable emphasis.



FIG. 8. Diodrast studies, February 20, 1946, showing vena cava still obstructed and the vena azygos enormously dilated and tortuous.

By diodrast visualization a complete obstruction of the superior vena cava and extensive collateral circulation involving particularly the azygos and mammary veins was demonstrated. For the following reasons the obstruction seems definitely to be located below the opening of the azygos into the superior vena cava: (1) diodrast shows continuity between the left

axillary, subclavian, and innominate veins, superior vena cava and azygos (figure 8); (2) the blood flow is clearly in reverse direction around the obstruction, reaching the heart by way of the inferior vena cava. If the obstruction was above the azygos opening, the direction of blood flow would be normal and the azygos would not fill with diodrast.



FIG. 9. Film taken two seconds after the film in figure 8, showing diodrast in lung fields, indicating satisfactory function of collateral system.

This case shows the azygos to be the important collateral system in superior vena caval obstructions below the azygos opening. Robb<sup>150</sup> also was able to visualize by angiocardiograms a similar collateral system in a case with similar point of caval obstruction. Carlson<sup>149</sup> was unable to demonstrate this system experimentally in dogs following ligation of the superior vena cava below the azygos opening. His animals died promptly of respiratory failure following this procedure. However, the two clinical cases cited above prove that superior vena caval obstruction below the azygos

opening is compatible with life. In view of Carlson's work this compatibility is probably dependent upon the time factor, requiring slow development of the obstruction, thereby allowing gradual and adequate formation of collateral circulation.

From an exhaustive review of the literature, this apparently is the only case on record in which coincidental obstruction of the trachea and the



FIG. 10. Film taken February 21, 1946, showing clear lung fields, indicating the shadows in figure 9 to be diodrast.

superior vena cava has been successfully operated upon. A female, age 40, having obstruction of both the superior vena cava and trachea, was operated upon by LeFort,<sup>72</sup> but died during surgery. Postmortem examination showed the obstructing mass to be a lymphosarcoma.

*Case 2.* M. S., a 29 year old white male, a garage mechanic by occupation, was seen December 15, 1942, complaining of vertigo and a sensation of fullness and pressure in the head and neck when exerting himself or stooping over. He had been well until the spring of 1942, when he suffered an attack of severe chills, feverishness, prostration, cough, and sore throat; he was ill for one week and saw no physician.

In July of that year he developed a vague malaise and noted vertigo when bending forward. These symptoms persisted until October, at which time he undertook a course of vigorous physical exercise and began to feel extraordinarily well. After several weeks, however, the vertigo on stooping returned and he also noticed swelling of the neck and simultaneously a mild choking sensation with dyspnea. Walking about slowly gave some relief; lying supine greatly aggravated the symptoms; a hot shower caused the symptoms to appear. In the two month period, ending in October, the collar size had increased from 14½ to 16. Two days prior to examination he engaged in a friendly scuffle with a fellow employee; he felt his neck swell, he became dizzy and dyspneic, and then, without losing consciousness, "everything went black."

Physical examination revealed a muscular and well nourished man with no abnormal cervical venous distention but with capillary varices over the upper sternum and a flushed face. The neck appeared large but showed no pitting edema and no tumors. Blood pressure in the arm was 150/88, in the leg 162/110. Funduscopy examination and the remainder of the physical examination revealed no abnormalities. Routine blood count and urine examination gave normal results; the basal metabolic rate was minus 9 per cent. A roentgenogram of the chest showed a fairly extensive calcification of both hilar regions with a calcified primary focus in the right lung.

No change in condition occurred during the following two months except that the capillary varices over the sternum became more extensive. Antecubital venous pressure determination taken February 8, 1943, was 17 cm. bilaterally. The latter half of February and the month of April 1943 saw an increase in symptoms and signs: mild exercise produced a greater degree of head fullness, dizziness and dyspnea than formerly; two pillows were necessary in sleeping.

Roentgenograms in April revealed a small traction diverticulum of the esophagus. Adjacent to the diverticulum was a mulberry-like calcification forming a mass 18 by 35 mm. in the right mediastinum opposite the aortic arch. The mass produced a definite paramediastinal bulge and was located just anterior to, and to the right of, the trachea. In this position, it was apparent that the mass and the superior vena cava were in very intimate relationship. There were other smaller calcified densities scattered throughout the mediastinum. The roentgenologist was of the opinion that the observed mediastinal densities represented calcified tuberculous lymph nodes.

Antecubital venous pressure readings, taken April 16, 1943, revealed a pressure of 27 cm. in the right arm, 24 cm. in the left. The lower extremities were normal in color and size, showed no pitting edema nor abnormal venous distention. The external jugular veins were dilated to a height of 12 cm. (vertical) above the manubrium sterni, with the patient in a standing position. The upper one half of the thorax was of a dusky color, the ear lobules were cyanotic, the face flushed, the lips livid, the retinal vessels moderately dilated, and the conjunctivae suffused. Many purplish tortuous capillary varices were present over the sternum, around the nipples, and on the lower anterior and lateral thorax bilaterally; less marked varices of the same type were found extending from the lower neck over the clavicle toward the sternum. Blood pressure in the arm was 132/78. The circulation time, using calcium gluconate in the "arm to throat" test, was 10 seconds.

This man has not been seen since April 1943. The etiology of the caval obstruction remains obscure. There are three possibilities: (1) chronic fibrous mediastinitis resulting from antecedent respiratory infection some three or four months prior to onset of symptoms, (2) chronic fibrous mediastinitis of tuberculous origin, (3) traction diverticulum of the esophagus. The evidence at hand favors chronic fibrous mediastinitis from respiratory infection. At least the causal relationship of this factor as regards time interval seems quite definite.

Both cases which we have reported emphasize the apparent etiological importance of respiratory tract infection in the development of chronic fibrous mediastinitis. On the basis of known facts pertaining to anatomy and bacteriological and pathological reactions, the theoretical sequence of events in such cases is: (1) respiratory tract infections (usually pneumonia); (2) lymphadenitis of mediastinal lymph node chains; (3) perilymphadenitis; (4) healing or chronicity with mediastinal fibrous tissue deposition; (5) cicatricial tissue contraction and partial obstruction of the superior vena cava; (6) thrombosis of superior vena cava, if the lumen becomes quite narrow and the intima becomes damaged or irregular.

### DISCUSSION

Available historical data indicate that William Hunter, 1757, published the first authentic account of a case of obstruction of the superior vena cava.

In the literature since 1904 there are at least 250 cases of superior vena caval obstruction.

Collateral diversion of the blood stream in the upper one-half of the body is responsible for some of the prominent clinical manifestations of the condition in question. The four principal collateral systems involved are defined and are presented in one composite, schematic representation, thereby showing their interrelationship and their relative importance in superior vena caval obstruction at different levels.

The anatomy of the mediastinum as regards the relationship of the superior vena cava to the ascending aorta, right bronchus, and lymphatic system is emphasized. The importance of disease of these structures in producing superior vena caval obstruction is indicated. It is shown that most of the structures of the right thoracic cavity and a part of the structures of the left thoracic cavity and mediastinum eventually drain into either or both the right anterior mediastinal and the right latero-tracheal lymphatic chains. The frequency of neoplastic and inflammatory disease in this part of the body is a constant threat to these lymph glands with possible obstruction, partial or complete, of the superior vena cava from extrinsic pressure or invasion. Chronic fibrous mediastinitis may result from inflammatory involvement.

So-called "idiopathic," or non-specific, chronic fibrous mediastinitis is probably secondary to such factors as trauma and pulmonary infection, particularly the latter, in a high percentage of cases. The time interval between the pulmonary infection and development of superior vena caval obstruction may be months or years.

There is a dramatic drop in incidence of syphilitic mediastinitis from 28.6 per cent to 0.9 per cent during the period 1904 to 1946. This apparently is a result of improved methods in the diagnosis and treatment of syphilis. There is a definite but less dramatic drop in incidence of tuberculous mediastinitis. Chronic fibrous mediastinitis of unknown cause was not

reported as such prior to the 1922 to 1933 period. From 1922 to 1946 the incidence increased from 5 per cent to 11.7 per cent. In view of probable importance of acute respiratory tract infection in the etiology of idiopathic, or non-specific, chronic fibrous mediastinitis and in view of the present effectiveness and availability of sulfonamide and antibiotic therapy, it is reasonable to suppose that future statistics will show a definite drop in incidence of this condition.

The etiological factors are tabulated, giving bibliographic references for each factor, and case reports divided into verified and unverified groups covering the period 1904 to January, 1946, inclusive. Comparisons are made with Fischer's series prior to 1904 and composite figures for both series tabulated. These tabulations indicate that 75 to 80 per cent of cases of superior vena caval obstruction are due to chronic mediastinitis, malignant primary thoracic tumors, and aneurysms.

Although there are conflicting opinions, there is considerable evidence that obstruction of the superior vena cava is not uncommon. The frequency of space occupying lesions of the mediastinum, the anatomical relations of the superior vena cava, the easy compressibility of this vessel, and the increasing number of case reports in the literature indicate that the syndrome probably occurs not infrequently.

Two cases of chronic fibrous mediastinitis are presented, one verified by surgery, both apparently a result of previous acute respiratory tract infection.

In case 1 the point of obstruction of the superior vena cava is demonstrated by angiocardiograms to be below the azygos opening, proving the lesion in this location to be compatible with life. The azygos is shown to be the important collateral system in caval obstructions below the azygos opening.

### SUMMARY

Literature for the period 1904 to 1946 was reviewed and 250 authentic cases of obstruction of the superior vena cava were found, 145 verified by autopsy or surgery.

Bibliographic data are tabulated according to etiology (table 3). Comparisons are made with Fischer's collection of 252 cases prior to 1904 and composite figures presented covering total incidence of important etiological factors in 502 cases from the world's literature to January 1946 inclusive.

The first authentic case report was by William Hunter in 1757.

Applied anatomy of superior vena caval obstruction is presented and particular emphasis given to collateral circulatory routes and the mediastinal lymphatic system.

Trends in etiology in the past four decades are discussed.

Special consideration is given to idiopathic, or non-specific, chronic fibrous mediastinitis and two case reports of superior vena caval obstruction resulting from this condition are presented. In one, the point of obstruction

is below the azygos opening into the superior vena cava and the principal collateral system is shown to be the azygos.

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# THE URINARY EXCRETION OF CREATINE IN ARTHRITIS \*

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THE investigation here reported was undertaken to ascertain whether or not there was any abnormal excretion of creatine in rheumatoid and osteoarthritis. Within the last decade, creatine metabolism has been the object of very extensive research. The mechanism of the intermediate metabolism of creatine has not yet been elucidated completely. Evidence, however, exists to favor the view that glycine is converted to guanidinoacetic acid which is then methylated to form creatine.<sup>1</sup> The first of these reactions probably takes place principally in the kidney and the transfer of free methyl groups occurs chiefly in the liver.

Considerable material has been gathered with regard to the occurrence of creatinuria under physiological and pathological conditions. It is present in childhood.<sup>2</sup> It is common in normal adult women especially during and immediately after the menstrual period.<sup>3</sup> While some authors have found no urinary creatine in the normal adult male, others have found creatinuria up to 200 mg. a day.<sup>4, 5, 6</sup> In an experiment it was shown by Taylor and Chew<sup>6</sup> that the protein intake had no influence on the creatine excretion. Primarily, creatinuria is encountered in progressive muscular dystrophy, tabes dorsalis, transverse myelitis, spinal cord tumor, encephalitis, chorea and myasthenia gravis. It is also frequent in febrile diseases, carcinoma, cirrhosis of the liver, cardiac failure, diabetes mellitus and hyperthyroidism.<sup>3, 7, 8</sup>

## CLINICAL MATERIAL

The material selected consisted of adult male and female subjects with no evidence of neurological involvement. During the period of the study the patients were on an ordinary diet. Four groups of subjects were studied. The first comprised 10 young adults, all normal. The second group of 10 patients varied in age from 48 to 87 years, and were relatively normal. The third group consisted of 10 patients under treatment for rheumatoid arthritis. The last group comprised 10 patients suffering from osteoarthritis. None of these subjects had any condition previously noted which might complicate the results.

## METHOD

All the subjects were on a regular diet and performed no unusual exertion on the day of the test. At 7:00 a.m. on the morning of the test, the bladder

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The laboratory work was done at the New York Post-Graduate Medical School and Hospital.

was emptied and the urine discarded. From 7.00 a.m. to 7:00 a.m. the following day the urine was collected and preserved with thymol. Specimens containing protein, sugar, or formed elements were not accepted. Urinary creatine was determined by the method of Folin.<sup>9</sup>

### RESULTS

Table 1 shows that on an unrestricted diet, in 10 normal healthy male and female adults, 18 to 33 years of age, the 24 hour creatine excretion varied from 85 mg. to 280 mg. These subjects were free from any infection or other diseases and performed no unusual exercises during the period of the test. The average 24 hour creatine excretion was 161 mg.

TABLE I  
24 Hour Urinary Creatine Excretion In 10 Young Healthy Adults

Case	Sex	Age	Volume	Creatine
1	F	18	1425 c.c.	280 mg.
2	M	23	1520 c.c.	161 mg.
3	F	21	950 c.c.	143 mg.
4	M	24	1310 c.c.	104 mg.
5	M	23	1220 c.c.	268 mg.
6	F	26	1670 c.c.	114 mg.
7	F	20	1330 c.c.	119 mg.
8	M	25	850 c.c.	85 mg.
9	F	33	2150 c.c.	129 mg.
10	M	28	1150 c.c.	207 mg.
Average				161 mg.

Table 2 shows that the 24 hour creatine excretion in 10 elderly subjects, 48 to 87 years of age, varied from 63 mg. to 351 mg. of creatine. The average 24 hour creatine excretion was 185.1 mg.

TABLE II  
24 Hour Urinary Creatine Excretion In 10 Elderly Healthy Adults

Case	Sex	Age	Volume	Creatine
1	F	67	1440 c.c.	115 mg.
2	M	50	1280 c.c.	280 mg.
3	F	65	900 c.c.	171 mg.
4	F	63	1800 c.c.	270 mg.
5	F	87	700 c.c.	70 mg.
6	M	55	1050 c.c.	63 mg.
7	F	64	870 c.c.	235 mg.
8	M	48	1300 c.c.	351 mg.
9	M	72	1800 c.c.	198 mg.
10	F	58	1620 c.c.	98 mg.
Average				185.1 mg.



Table 3 shows that in 10 patients with rheumatoid arthritis, 31 to 62 years old, who had the disease from 1 to 20 years, the 24 hour urinary creatine excretion varied from 40 to 358 mg. and the average excretion was 175.9 mg. in 24 hours. In patients 8 and 10 it was observed that as the condition improved on gold therapy, the creatine excretion increased and was concomitant with a gain in weight and an improved sense of well being.

TABLE III  
24 Hour Urinary Creatine Excretion In Rheumatoid Arthritis

Case	Sex	Age	Duration	Creatine
1	F	38	13 years	216 mg.
2	F	34	8 years	98 mg.
3	F	53	20 years	252 mg.
4	F	62	5 years	196 mg.
5	M	41	7 years	40 mg.
6	F	36	12 years	91 mg.
7	M	31	1 year	76 mg.
8	F	45	10 years	262 mg.
9	M	62	6 years	170 mg.
10	F	35	10 years	358 mg.
Average				175.9 mg.

There appeared to be no correlation between the creatine excretion, blood cholesterol or sedimentation rate. Neither age nor the duration of the disease had any effect on the creatine output. In spite of the widespread nerve and muscular changes characteristic of rheumatoid arthritis, the average 24 hour creatine excretion in the 10 patients was within normal limits. Two

TABLE IV  
24 Hour Urinary Creatine Excretion In Osteoarthritis

Case	Sex	Age	Duration	Creatine
1	F	65	10 years	1498 mg.
2	F	44	3 years	719 mg.
3	F	36	9 years	639 mg.
4	M	50	10 years	741 mg.
5	F	59	2 years	611 mg.
6	M	68	15 years	700 mg.
7	M	70	40 years	434 mg.
8	F	72	10 years	448 mg.
9	F	53	1 year	502 mg.
10	F	56	1 year	462 mg.
Average				675.4 mg.

daily creatine determinations on a case of lupus erythematosus disseminatus were found to be within normal limits (262 mg. to 175 mg.).

In table 4 the youngest patient was 36 years and the oldest 72 years. The osteoarthritis had been present in these cases from one to 40 years. All of these patients had a normal sedimentation rate (Westergren). Here, the

creatine excretion varied from 434 mg. to 1498 mg. in 24 hours. The average 24 hour creatine excretion was 675 mg. None of these patients had any dietary restrictions. Alpha-tocopherol in large doses (300 mg. daily) was used for three months in the last three patients with no clinical improvement and with no effect on the creatinuria.

### DISCUSSION

From the evidence it appeared that creatinuria was a normal process in the adult male and female and that it occurred in all the age groups of the above investigation. In tables 1 and 2 the average normal 24 hour urinary creatine was less than 200 mg. It is stated that "creatine is normally absent from the urine of men."<sup>10</sup> Creatine was never absent in any of the groups. It is possible that inadequate methods and lack of proper equipment could explain the failure of earlier workers to observe creatinuria in the normal adult male.<sup>11</sup>

Table 3 indicated that this group with active rheumatoid arthritis had a normal creatine excretion.

Table 4 showed an increase in the average creatine excretion for the patients with osteoarthritis. The creatinuria could not be explained by muscular atrophy since very few of the patients examined showed any signs of this condition.

### CONCLUSIONS

In a young group of 10 normal subjects ages 18 to 33, male and female, the average creatine excretion was 161 mg.

In an older group of 10 healthy subjects whose ages varied from 48 to 87 years the average 24 hour creatine excretion was 185.1 mg.

The average creatine excretion in 10 subjects with active rheumatoid arthritis was 175.9 mg.

In 10 patients with osteoarthritis, the 24 hour creatine excretion averaged 675.4 mg.

The possibility is presented that in osteoarthritis there exists an abnormal excretion of creatine.

I am indebted to Dr. Edward F. Hartung for his helpful suggestions.

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# NEUROCIRCULATORY ASTHENIA \*

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THE more symptoms a patient complains of, the less the significance of each. Every paper on the subject of Effort Syndrome from the day of DaCosta<sup>1</sup> to the present,<sup>2, 3, 4, 5</sup> has stressed the multiplicity of the symptomatology. MacKenzie<sup>6</sup> has pointed out the difficulty in describing the most common forms of disease, perhaps because of the fact emphasized by Starr<sup>7, 8</sup> that it may be no disease but an exaggerated physiology or what has been referred to in a previous publication<sup>9</sup> as a physiogenic form of abnormality of adjustment. Starr ingeniously compares effort syndrome with ordinary clumsiness of muscular movement inferring that his ballistocardiographic studies are an excellent method of studying objectively this particular clumsiness of the circulation. He further states<sup>10</sup> that the group ordinarily diagnosed as neurocirculatory asthenia shows an incoördination of the circulation which brings his analogy from mere clumsiness toward what might be termed "ataxia" of the circulation. And it is true that all variations are seen from mildly exaggerated physiological response to exercise to a state of extreme disability.

Levy, Stroud and White<sup>11</sup> in their reëxamination of men disqualified for military service because of cardiovascular defects found that 17.3 per cent could be reclassified as fit for duty. They felt that neurocirculatory asthenia was a legitimate cause for rejection and this condition accounted for 4.9 per cent of those rejected for cardiovascular defects. In our experience neurocirculatory asthenia accounts for 6.8 per cent of the admissions to the cardiovascular section of a large general hospital in the United States; 4.6 per cent of the admissions to a comparable unit in the European Theater of Operations and 6.3 per cent of the admissions to the cardiovascular section of a Regional Hospital in the United States. These figures are based on the admission of 30,000 patients. Many of these patients were referred to the cardiologist by the neuropsychiatrists and from other wards in the hospital. Those with manifest anxiety were usually received on the neuropsychiatric wards with a label of combat exhaustion. These cases were usually seen with the psychiatrist and treated with the other cases of exhaustion. If symptoms were severe and persistent they were given a careful cardiac examination with electrocardiographic, phonocardiographic<sup>9</sup> and fluoroscopic methods to determine the presence or absence of organic heart disease.

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## ANALYSIS OF DATA

In 75 per cent of the cases the duration of the disease was 10 years or more and consequently was felt to have existed prior to enlistment. In the remaining 25 per cent the condition had not caused symptoms prior to military service. In many cases the individual had been limited in his physical activity prior to entering the army and he had chosen to follow a more or less sedentary job probably because attempts at hard work had shown him to be poorly fitted for such occupation. This is consistent with the findings of Lewis,<sup>3</sup> Starr<sup>8</sup> and others.<sup>12</sup>

In the entire series there were 576 patients admitted with a diagnosis of neurocirculatory asthenia or effort syndrome. These were classified into one of the following groups:

- I. Those with stigmata of constitutional inadequacy.
- II. Those with poor physical endowment plus anxiety.
- III. Those with primary neurotic manifestations.

It was recognized that no sharp line of distinction could be drawn but by far the majority, 69 per cent, fell into the Group II description and this was much more apparent among those received in hospitals in the European Theater either before entering combat or those who quickly broke down when thrown into combat. In Group I were 14 per cent more of whom were seen in the United States, and 17 per cent fell into Group III about half of whom were seen in the United States and the other half in the combat zone.

By far the majority, 77 per cent, were of the asthenic type and inclined to be underweight as judged by standards of the Medico-Actuarial Mortality Investigation.<sup>13</sup> The average age was 24.7 years. They averaged 8.9 pounds below ideal weight. A few, 8 per cent, were above normal weight and 15 per cent were within normal range. There was no great increase in the number of previous severe infections in this group as compared to other hospital patients, but 8 per cent gave a history suggestive of rheumatic fever or severe sorethroat, and 12 per cent considered themselves subject to "colds" and upper respiratory infection. A fair number of those with neurocirculatory asthenia had been previously hospitalized for jaundice, pneumonia or shell-fragment wounds (21 per cent). Very few of these men, 11 per cent, had been told at some time previously that they had a heart murmur or that their blood pressure was a little too high. A few, 3 per cent, had been kept in bed for a prolonged period because of supposed "heart disease" as a child or prior to their army service.

A considerable number of patients, 19 per cent, gave a history of acute onset of symptoms following sudden exertion or excessive physical strain such as is involved in combat and extreme hardship. Of these the majority occurred early in their combat experience. A good many became conscious of their first symptoms coincident to sea-sickness while the mere threat of going into combat was frequently enough to precipitate the initial attack.

In the majority of these cases there was a great blending of emotional and physical factors either of which was sufficient to explain the reaction.

A small number of patients, 4.2 per cent of the total, showed evidence of a co-existing cardiac lesion. The order of incidence was as follows: mitral stenosis, aortic insufficiency, congenital heart disease, cardiac enlargement, paroxysmal auricular tachycardia, paroxysmal auricular fibrillation, ventricular extrasystoles, and hypertension.

### SYMPTOMATOLOGY

A fairly large number of the patients seen in the combat zone also suffered with trench-foot or frost-bite (21 per cent) and it seemed to some observers that there was an etiological relationship between the two pathological conditions. Some of the psychiatrists considered that the patient with neurocirculatory asthenia would be hyper-susceptible to trench-foot or frost-bite because of his maladjusted circulation. In fact cold feet was a common complaint among these patients, often a more bitter complaint than the breathlessness that is usually considered the most common symptom. Breathlessness and hyperventilation at rest did occur in some cases but was not as common as reported by others.<sup>14, 15</sup> With exertion breathlessness was a constant symptom and this could often be simulated by excitement. Response to exercise was always poor and the Schneider Index<sup>16</sup> is useful in bringing out the orthostatic hypotension and poor index which will almost always be below 5. The greater the exercise the more severe the symptoms. They are almost completely relieved by rest. This is the reason the term "physiogenic" has been suggested because the symptoms are easily produced physiologically and can be relieved the same way.

Fatigue and exhaustion are often apparent in the facial expression and in the weakness manifest by a general droopiness in posture and activity. The tremor and shakiness increase with the degree of fatigue. Light-headedness, a feeling of faintness, and mild subjective vertigo were common, often precipitated by the erect posture and/or exercise and relieved by rest in the recumbent position. These symptoms were usually readily produced by the performance of the tilt-table test.<sup>9, 17</sup> In fact, in the early portion of our series it was considered almost a prerequisite to the diagnosis of neurocirculatory asthenia to produce the syndrome in the tilt-position.<sup>9</sup> Haldane<sup>18, 19</sup> states that the abnormal breathing observed in neurocirculatory asthenia is due to fatigue of the respiratory center induced by anoxia.

In a series of well written articles, Friedman<sup>20</sup> has brought forward the thesis that the symptoms of neurocirculatory asthenia stem from hypothalamic dysfunction which in turn causes an excitation of the sympathetic nervous system as described by Fraser and Wilson<sup>21</sup> in their study of the pathogenesis of the syndrome. Cannon<sup>22</sup> pointed out the similarity between neurocirculatory asthenia and the fear or rage reaction in animals following stimulation of the sympathetic nervous system. Friedman has also similarly explained the profound vasoconstriction as a cause of the hyperthermia

and giddiness so frequently complained of and noted by Lewis,<sup>3</sup> Cohn,<sup>23</sup> and Parkinson<sup>24</sup> in accordance with the concepts promulgated by Ransom.<sup>25</sup>

Precordial pain was a complaint in 56 per cent of the cases in this series. It was usually described as occurring in the left side of the chest and more often than not it was an aching or a feeling of soreness accompanied by hyperalgesia. Among those cases seen in the combat zone there was a definite tendency for the pain to be described by the patient in accordance with the lay ideas of angina pectoris or to mimic the stories given by patients with definite coronary disease when it was learned that this frequently led to a transfer to a hospital in the zone of the interior (United States). Sometimes these stories were actually of textbook clarity and were, therefore, of little value in actual assessment of disability. The multiplicity of symptoms and the clinical evidence of either neurocirculatory asthenia or organic heart disease had to be depended upon in a large measure for accuracy in diagnosis. Palpitation, fainting, giddiness, sweating, acrocyanosis and other peripheral signs were of great value in the differential diagnosis.

Electrocardiographic changes, while not specific,<sup>26, 5, 9, 27, 28, 29, 15</sup> were indeed helpful especially when a maneuver such as the erect position, tilting, Schneider Index, and other functional tests were utilized. In this series of cases 35 per cent showed some deviation from normal in records taken before and after exercise or before and after tilting.

Physical signs were usually limited to tachycardia and tachypnea, overactive heart action, unstable blood pressure, a quick and often roughened first heart sound at the apex, cold sweating extremities, and gross evidence of anxiety such as fluttering eyelids, tremor, pallor of the face, excessive pulsation in the neck, insomnia, and nightmares. There may be co-existing neurasthenia, hypochondriasis, hysterical substitution or conversion. Mild depression or mental irritability may predominate.<sup>30</sup> Knehr, Dill and Neufeld<sup>31</sup> feel that blood lactate studies may be useful in the determination of cardiovascular fitness. The studies of Robinson and Harmon brought out a fairly clear distinction between the findings in young men with poorly adaptable circulatory systems and first class athletes.<sup>32</sup> MacLean<sup>33</sup> treated patients with unstable vasomotor systems manifesting orthostatic tachycardia and hypotension by the use of the "head-up" bed and increased salt intake with marked improvement in their adaptation to the erect posture. This phenomenon further substantiates the opinion that disturbed physiology exists in this condition and that the symptoms are physiogenic in origin.

Increased interest in the disturbed physiology of individuals who are subject to neurocirculatory asthenia has followed the demonstration by Cobb, Cohen and Badal<sup>34</sup> of the increased number of twisted capillaries in the nail folds of 48 patients studied. This discovery brings to the fore once again that we are dealing with a condition in the "borderland of disease" to quote Lewis,<sup>3</sup> which when thoroughly understood constitutes an ideal psychosomatic disease for the coordinated study of physiologists, psychiatrists, psychologists, neurologists, endocrinologists<sup>35</sup> and internists.

## PRINCIPLES AND METHODS OF TREATMENT

It was certainly with pardonable pride that Sir Thomas Lewis<sup>36</sup> refers to his greatest contribution to what is now called Physical Medicine Rehabilitation, as follows: "It was at Hampstead that a system of graded drills was first introduced, and later I employed these to the full both remedially and as a means of justly grading soldiers returned to hospital for supposed affections of the heart. It was my repeated contention that the surest means of gauging physical fitness and endurance is to employ direct tests." This method was utilized both in this country and abroad in the handling of patients with neurocirculatory asthenia. The results were gratifying and effective almost in direct proportion to the completeness with which the original medical work-up was accomplished and the thoroughness of the examiner as well as his powers of persuasion and ability to establish rapport with his patients. It was found to be an excellent policy in our series as well as those treated by Hill and Dewar<sup>37</sup> to forbid further medical examinations or the taking of pulse rates, blood pressure or temperature once the original complete examination was finished. This gave no further suggestion to the patient that anything but recovery was expected. Graduated physical exercise and reassurance by all concerned was the keynote of treatment. Exercises were started with easy drill and physical exercise under careful supervision. Progress was required but it could be slow for some groups and more rapid for others.<sup>38</sup> Group psychotherapy<sup>39</sup> was found to be most helpful in the hands of physicians possessed of the necessary orientation and ability. Privilege rewards for accomplishment were considered extremely helpful in keeping up the interest of participants. Cases not making satisfactory progress were counseled by the psychiatrist and those responding well were discharged from the hospital without further examination. A fairly high percentage of the Group III cases required transfer to a Neuropsychiatric Rehabilitation Center.<sup>40</sup>

## RESULTS

It has been impossible to follow-up all of the cases reported in this paper. The immediate results of treatment were gratifying. Of the cases seen in the United States during the years 1941 and 1942, the large majority (72 per cent) were discharged from military service,<sup>41</sup> while 20 per cent were sent to limited duty and 8 per cent were returned to full duty. In the European theater, 40 per cent were returned to full duty, 16 per cent to limited duty, 33 per cent were referred to the neuropsychiatric rehabilitation center, and 14 per cent were returned directly to the United States. From reports received from the neuropsychiatric rehabilitation center where more adequate and longer periods of treatment for the underlying anxiety were undertaken, the total number returned to duty, either light or full military duty, would approximate 75 per cent. No figures are available by which it could be determined how many of these cases relapsed after treatment but



it was not unusual for us to treat the same veteran a second time after his original return to duty. By far the majority of these men responded well to treatment and when returned to duty fairly soon seemed to adapt better. Prolonged hospitalization and separation from their combat unit disturbed their morale and prolonged their rehabilitation.

### SUMMARY

The pathogenesis of neurocirculatory asthenia has been studied by a great many careful observers and specialists in various fields of medicine. That the symptoms can be produced physiologically in susceptible individuals has been shown conclusively. It has also been shown that the symptoms are usually relieved by physiological rest and measures directed toward improved physical adaptation. Methods for the detection and differential diagnosis have been discussed and the problem from a military standpoint is reported. Experience with a large number of patients suffering with this manifestation of a psychosomatic disease has undoubtedly served to familiarize many physicians with a practical method of dealing with these daily problems.

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# TREATMENT OF MALIGNANT DISEASE WITH NITROGEN MUSTARD \*

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OUR purpose in this paper is to summarize the clinical literature on the use of the nitrogen mustards in malignant diseases,—the indications, hazards, effects and side-effects. Our experience with 64 additional cases is included.

Reports on the clinical application of the nitrogen mustards in the treatment of neoplastic diseases have recently been released.<sup>1</sup> Rhoads<sup>4</sup> summarized the results of therapy as follows:

1. Methyl-bis ( $\beta$ -chloroethyl) amine hydrochloride (designated HN2) appears to be preferable to tris ( $\beta$ -chloroethyl) amine hydrochloride as venous thrombosis is less likely to follow at the injection site.

2. The recommended dosage is 0.1 mg. per kilogram intravenously on four successive days. Larger doses proved to be hazardous.

3. The toxic effects noted are:

## A. Local

1. Severe local inflammatory reaction if extravasation into the tissues occurs.

2. Thrombosis and thrombophlebitis.

## B. Systemic

1. Nausea and vomiting occurring one to eight hours after a single dose and continuing for three to 24 hours; occasional diarrhea.

2. Damage to the blood forming organs, characterized by
  - (a) Leukopenia (lymphopenia followed by neutropenia)
  - (b) Normocytic anemia
  - (c) Thrombocytopenia, at times accompanied by bleeding.

4. Cure of neoplastic diseases has not been observed; tumor regressions have been only temporary, rarely extending beyond several months.

The most favorable results, according to Rhoads, have been obtained in the treatment of Hodgkin's disease. Improvement, evidenced by reduction in the size of lymph nodes, disappearance of fever, feeling of well-being and weight gain, usually continued for from two weeks to a few months, followed by fairly rapid relapse. Relapses often responded to further chemotherapy, but remissions were progressively shorter in duration. The

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liver and spleen usually regressed only slightly in size. Large masses of matted lymph nodes, invasion of the disease beyond lymph nodes, and bone lesions often did not show a favorable response even though symptomatic improvement occurred. Skin lesions due to Hodgkin's disease responded variably, and pruritus was only occasionally and slightly relieved. In late, roentgen-ray-refractory cases, HN2 was occasionally of benefit. Highly malignant lymphosarcoma usually failed to respond. Most cases of giant follicular lymphoblastoma improved, but the Committee on Growth recommended local roentgen-ray therapy as the treatment of choice. Acute lymphoblastic and myeloblastic leukemias were not influenced by the drug. Chronic lymphatic leukemia usually responded with a reduction in the white count, decrease in size of the lymph nodes, with somewhat less effect on the hepatosplenomegaly. Since a fall in hemoglobin may also occur, the drug was not recommended in far advanced cases with severe anemia. Chronic myelogenous leukemia was usually similarly affected, but Rhoads preferred local roentgen irradiation for greatly enlarged spleens. Results with polycythemia vera were comparable to those obtained with radioactive phosphorus. Suggestive favorable experience with the production of temporary symptomatic remissions in anaplastic carcinoma of the lung has been reported. Melanosarcoma, metastatic mammary and uterine cervical carcinoma, and multiple myeloma have not responded favorably. Two cases with metastatic sympathicoblastoma<sup>8</sup> responded with rapid reduction in the size of the tumor masses; but remissions were only short-lived.

Jacobson et al.<sup>3</sup> determined urea clearance, plasma proteins, albumin and globulin ratio and cholesterol (total and esters) before and after treatment. No significant changes were noted, whether or not the original values were abnormal. These observers reported leukopenia beginning within 24 hours after the first injection and progressing for three to eight days. Recovery from the leukopenia was not influenced by pentnucleotide, ferrous adenyate, leukocytic extract, or folic acid. Despite marked leukopenia, infection occurred in only one of 59 cases. The infection responded satisfactorily to penicillin therapy. Urobilinogenuria indicated significant increase in hemolysis, but the hemoglobin rarely fell significantly except in polycythemia. The reticulocyte count regularly fell below 0.1 per cent. Marked thrombocytopenia occurred variably. Marked aplasia of the bone marrow, always followed by regeneration, was common. In a supplementary report, Jacobson's group<sup>5</sup> reported on the quantitative findings in sternal marrow aspirates in five cases treated with HN2. The nucleated cell count fell to a minimum during the first two weeks and returned to normal by the sixth week. These authors noted many giant granulocytes in the peripheral blood during the first week.

Goodman et al.<sup>2</sup> whose 67 cases of Hodgkin's disease, leukemia and allied disorders are included in Rhoads' <sup>4</sup> summary, drew particular attention to the usually good results in the treatment of Hodgkin's disease even when the disease had become refractory to radiation. Of 13 patients with lympho-

sarcoma, nearly all in advanced, radio-resistant stages, five failed to improve and in the others the remissions lasted from three weeks to several months; but with each recurrence the course of nitrogen mustard proved less effective and the remission produced was shorter-lived. The authors also found that repeated urinalysis, renal and liver function tests and blood chemistries failed to indicate any change due to therapy with the nitrogen mustards. In the two patients who were treated with more than 0.1 mg. per kilogram for three to six doses (maximum single dose 8 mg.), "toxic hemopoietic effects were observed in the following sequence: the complete disappearance of circulatory lymphocytes, definite leukopenia and granulocytopenia (without mucosal lesions or other signs or symptoms of agranulocytosis except fever), thrombocytopenia of severe grade with purpura, and moderate anemia. Repeated blood transfusions were necessary, and the return of blood values to pre-treatment levels required several weeks."

Wintrobe et al.<sup>8</sup> treated 77 cases of lymphoma with doses varying from 0.1 mg. to 0.25 mg. per kilogram daily in courses of four to eight injections. There were no toxic deaths. Their results were in general agreement with those reported by other members of the group coöperating with the Committee on Growth as detailed above. Two patients with metastatic carcinoma responded with temporary regression of metastatic nodes and improvement in symptoms. The authors noted promising results with the use of "maintenance therapy," consisting of two injections every two to six weeks in lymphomatous patients in remission.

The several series reported above were studied in coöperation with the Committee on Growth and formed the basis of Rhoads' summary.<sup>4</sup> Several smaller series have been reported independently. Alpert and Peterson<sup>6</sup> treated 23 cases of malignancy. Their 15 cases of Hodgkin's disease showed variable response. Post-treatment biopsies revealed necrosis of the reticulum cells, Sternberg-Reed cells and eosinophiles. One case of bronchogenic carcinoma responded with slight shrinkage of the tumor and clearing of hydrothorax, but death from metastases ensued. ApThomas and Cullumbine<sup>7</sup> obtained remissions averaging two months' duration in 21 cases of Hodgkin's disease treated with HN2. They found that 0.2 to 0.3 mg. per kilogram for two days produced the same effects as 0.1 mg. per kilogram for four days with the advantage of fewer days of discomfort for the patient. The two patients treated with 0.2 mg. per kilogram for four days developed severe leukopenia (below 1,000 per cu. mm.), but the counts returned to normal in two weeks without untoward symptoms. Osborne et al.<sup>9</sup> treated five cases of cutaneous lymphomatous disease. They noted marked temporary improvement in mycosis fungoides and cutaneous lymphosarcoma, but no response in the one case of Kaposi's sarcoma treated. They noted marked improvement in a case of chronic disseminated lupus erythematosus. Kierland and Shullenberger<sup>10</sup> also treated six cases of mycosis fungoides with improvement in five for periods up to four months. Taffel's<sup>11</sup> observations on 16 cases of neoplastic diseases are in agreement with those

reported previously. He administered the standard dose of 0.1 mg. per kilogram. Six patients developed pronounced thrombocytopenia, with hemorrhagic phenomena in five. Included in this series were one case of embryonal carcinoma of the testis and one case of fibrosarcoma of the chest wall. Neither patient was benefited by HN2 therapy. An adolescent with a metastatic Ewing tumor of the pelvic bone improved slightly after HN2 treatment, but relapsed promptly.

### CLINICAL RESULTS

This paper reports our observations in the treatment of 64 cases of malignant diseases with HN2 \* in the period between July 1946 and January 1948. The cases may be classified as follows: 24 Hodgkin's disease, four chronic lymphatic leukemia (including one associated with lymphosarcoma and one with Hodgkin's disease), two chronic myelogenous leukemia, 10 carcinoma of the lung, two Wilms' tumor, one carcinoma of the breast with generalized metastases, one anaplastic metastatic carcinoma, one melanocarcinoma, eight lymphosarcoma, two mycosis fungoides, one chronic non-leukemic myelosis, three reticulum cell sarcoma, one spindle cell sarcoma, one miliary tuberculosis, one Boeck's sarcoid, and two malignancies of undetermined nature. All of these patients were treated with methyl bis ( $\beta$ -chloroethyl) amine (HN2) in the usually recommended dose of 0.1 mg. per kilogram on each of four successive days, except for eight patients who received 10 mg. daily for four consecutive days. Twenty patients received from two to six courses. In the first half of the series complete blood counts and urinalyses were performed daily, sternal myelograms were performed before, immediately after, and two weeks post-treatment, as were bleeding studies, liver and renal function tests, gastric analyses, sedimentation rates, and blood chemistries (urea nitrogen, sugar, uric acid, creatinine, calcium, phosphorus, alkaline phosphatase, cholesterol, cholesterol esters, total protein, A/G ratio). The only changes noted were in the peripheral blood picture in practically every case and in the myelogram in one case (Case 48) (total nucleated bone marrow counts were not done). In the later cases, only the blood picture was followed routinely because of the negative results obtained in the first group.

*Hodgkin's Disease:* The results with Hodgkin's disease are summarized in table 1. In all cases the diagnosis was established by lymph node biopsy. Sections made elsewhere were reviewed by the pathologists of this hospital. As is apparent from the table, temporary remissions were obtained in 20 of the 24 cases studied. Of the four complete failures one died on the second day of treatment of genito-urinary hemorrhage which had begun before admission, and cannot therefore be considered an HN2 failure. There were two toxic deaths. The first one occurred as a result of agranulocytosis and

\* The nitrogen mustard used in this study was supplied by Merck & Co., Rahway, N. J., on the approval of the Committee on Growth, National Research Council.

TABLE I  
Hodgkin's Disease

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage		Observation	Remission	
1	S. P.	29	F	1940	X-ray, good response until Sept. 1946	9/27/46	0.1 mg./K×4		3 months	2 months	Lymphadenopathy became x-ray resistant. Responded to HN2 with weight gain and general symptomatic improvement.
						12/18/46	0.1 mg./K×4		2 weeks	None	Died Jan. 1947 with agranulocytosis thrombocytopenia, esophagitis, proctitis, generalized hemorrhages due to HN2 toxicity. P. M. revealed fibrosis of lymph nodes. No evidence of Hodgkin's except a single nodule in spleen. See case report.
2	F. S.	33	M	1943	X-ray, good response until 1946, but developed draining sinuses. Became x-ray resistant early 1946. X-ray Oct. 1946—followed by increase in size of cervical nodes.  X-ray from Jan. to June 1947—improvement fairly well maintained.	7/22/46	0.1 mg./K×4		8 weeks	5 weeks	Rapid disappearance of pruritus after HN2. Moderate reduction of adenopathy. Marked subjective improvement. Ulcerations smaller, drainage less.
						9/27/46	0.1 mg./K×4		7 weeks	None	Much less effect from second course. Nodes slightly smaller.
						11/20/46 12/4/46 12/31/46	0.1 mg./K×4 0.1 mg./K×4 0.1 mg./K×4		6 months	5 months	No response to third course. Following fourth course, lymphadenopathy diminished, pruritus subsided, symptomatically improved. Ulcers healed but nodes increased after four weeks. After fifth course, marked decrease of nodes, diminution of pain and itching.
						6/12/47	10 mg.×4 (0.15 mg./K×4)		6 months	3 months	Moderate subjective improvement, decrease of edema of arms after sixth course. HN2 burn of foot healed in one month. Persistent anemia responded to transfusion. Admitted to chronic disease hospital, where in Dec. 1947 condition was poor. See case report.



TABLE I—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission		
3	W. S.	41	M	1944	None	8/23/46	0.1 mg./K×4	3 months	1 month	Marked response to HN2. Pel-Ebstein fever terminated abruptly. Lymph nodes smaller, good appetite, feeling of well-being.	
						12/5/46	0.1 mg./K×4	4 weeks	3 weeks	Marked improvement after second course. Mediastinal lymph nodes disappeared.	
						1/7/47	0.1 mg./K×4	5 weeks	3 weeks	Moderate improvement after HN2. Temperature dropped.	
						2/25/47	0.1 mg./K×2	4 weeks	3 weeks	Liver, spleen now palpable. Temperature drop after HN2 (possibly coincidental). Short course given because of low WBC and platelets.	
						3/20/47	0.1 mg./K×4	4 weeks	1 week	Drop in WBC accompanied by throat ulceration followed HN2. Responded to penicillin. Nausea, vomiting relieved for only one week. No response to transfusions. Died 4/16/47. P.M. findings—generalized Hodgkin's.	
4	M. S.	50	M	1937	X-ray, good response until 1944. Completely refractory in 1946.	10/11/46	0.1 mg./K×4	8 weeks	5 weeks	After HN2 marked reduction of cervical spine pain, slight relief of radicular pain of left arm. Nodes slightly smaller.	
						12/11/46	0.1 mg./K×4	6 months	3-4 months	No relief of pains or decrease of nodes following HN2. Relief obtained with added radiotherapy although previously x-ray resistant.	
					X-ray, March-April 1947, some improvement in ulcer. Reduction of arm edema.	6/9/47	0.1 mg./K×4	6 weeks	None	Spleen, nodes smaller, no other improvement from HN2. Patient transferred to chronic disease hospital Sept. 1947, died there Oct. 1947. P.M. findings—generalized Hodgkin's.	
5	S. H.	38	M	1942	X-ray, minimal response.	Sept. 1946	0.1 mg./K×3	None	None	Died during treatment with HN2 of exsanguinating hemorrhage from urinary bladder. P. M. findings—generalized Hodgkin's.	

TABLE I—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage		Observation	Remission	
6	A. G.	30	F	1940	X-ray 1945—moderate response. ACS injections 1946, very little response.	10/16/46	0.1 mg./K×4	2 months	6 weeks	Sister had Hodgkin's. Marked symptomatic improvement after HN2. Ascites, cough, pain disappeared. Adenopathy reduced. Edema, pleural fluid disappeared in two weeks.	
						12/19/46	0.1 mg./K×4	3 months	2 months	Marked but less striking improvement after second course. Stomatitis developed with low WBC, responded well to penicillin. Readmitted in March 1947 with severe recurrence. Little response to x-ray. Refused HN2 and signed out to another hospital, where progressive downward course continued until death 9/9/47. No P.M.	
7	R. S.	23	M	Oct. 1946	None	Nov. 1946	0.1 mg./K×4	10 months	>10 months	Excellent response to HN2. Dyspnea due to mediastinal adenopathy cleared. Nodes smaller. Improvement has been maintained following short course of x-ray.	
8	A. G.	22	F	1943	X-ray, good response until four months before admission.	Oct. 1946	0.1 mg./K×4	2 months	>2 months	Dramatic favorable response to HN2 with almost complete disappearance of nodes, abdominal and bone pains, lung infiltration and abdominal mass. Marked increase of appetite and well-being, no longer bedridden or cachectic.	
9	J. S.	31	M	1942	X-ray, minimal response.	Dec. 1946	0.1 mg./K×4	3 weeks	None	No effect of HN2 noted at time of discharge. No follow-up.	
10	C. S.	27	F	1936	X-ray 1936-1946—3 courses with remissions of 5 years, 3 years, 1 year, respectively.	12/7/46	0.1 mg./K×4	3½ months	2½ months	Marked symptomatic improvement after HN2. Decrease in size of liver, spleen, nodes. Increase in weight and hemoglobin. Recurrence of bone (back and leg) pain after 2½ months.	
						4/10/47	0.1 mg./K×4	5 months	2 months	Marked improvement with second course. Back pain subsided rapidly. Edema of leg cleared. X-ray resumed immediately after HN2. Anemia recurred in two months, responded to transfusions.	

TABLE I—Continued

TREATMENT OF MALIGNANT DISEASE

Comments

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		
						Date	Dosage	Observation	Remission		
10	C. S.	27	F	1936	X-ray April-Sept. 1947, maintained fair remission.	Sept. 1947	0.1 mg./K×4 Teropterin 5 mg. I.M. daily.	3 months	>3 months	Moderate response of fever, leg edema to HN2. Anemia still responsive to transfusions. Admitted to chronic disease hospital Oct. 1947. Steady downward course to present (April 1948).	
11	N. S.	17	F	July 1946	X-ray Sept.-Dec. 1946, minimal response.	Dec. 1946	0.1 mg./K×4	6 weeks	>6 weeks	Marked improvement in appetite and sense of well-being following HN2. Mediastinal mass and pleural effusion unchanged, but dyspnea relieved.	
12	E. C.	56	F	1940	X-ray, no response since 1945.	Nov. 1946	0.1 mg./K×4	1 month	None	No response to HN2. Pulmonary infiltration and hydrothorax persisted. Died four weeks after course of HN2. No P.M.	
13	M. G.	35	F	Nov. 1944	X-ray, fair response until one month before admission. X-ray, fair response for a few months.	Jan. 1947	0.1 mg./K×4	3 months	1 month	Good response to HN2. Complete relief of root pain. Nodes smaller. Pain recurred after one month.	
						April 1947	0.1 mg./K×4	6 months	1 month	Again transitory relief of pain after HN2. Recurrence treated with x-ray, with slight improvement.	
						Oct. 1947	0.1 mg./K×4	6 weeks	2-3 weeks	Partial relief of pain for few weeks after third course. Nodes slightly smaller. Has recently developed fever.	
14	H. R.	59	M	1945	X-ray at six month intervals with good response. No response of fever to x-ray, chemotherapy, or antibiotics.	2/4/47	10 mg.×4 (0.16 mg./K×4)	3 months	2½ months	Excellent response to HN2. Fever subsided promptly. Appetite and strength increased. Nodes, liver, spleen smaller.	
						5/20/47	0.1 mg./K×4	2 months	1 month	Excellent response again. Prompt drop in temperature, return of appetite, gain of weight and strength. Spleen no longer palpable, lymph nodes much smaller.	
						7/22/47	0.1 mg./K×3 Teropterin 5 mg. I.M. daily.	2 weeks	1 week	Course shortened due to sharp drop in WBC. Fever stayed down only eight days. No other improvement. Jaundice, leg edema and ascites now present. Psychosis finally led to transfer to psychiatric hospital.	

TABLE I—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage		Observation	Remission	
15	H. R.	40	F	July 1946	X-ray Oct. 1946, little effect on mediastinal mass. X-ray therapy to chest repeated Jan. 1947, moderate response of mass, but rapid relapse.	4/23/47	0.1 mg./K×4		6 weeks	3 weeks	Slight subjective improvement after HN2. Decrease of cervical nodes, not of mediastinal mass. No effect on chest fluid or fever. Relapse after three weeks, with progressive downward course.
16	E. B.	25	M	1945	X-ray, excellent response with many courses in 1945-1946. In 1947, progressive cord symptoms not halted by x-ray.	5/26/47	0.1 mg./K×4		3 months	3 months	Excellent response to HN2. Immediate effect after first dose, halting rapidly progressing cord symptoms, with regression of signs of cord compression. Remission maintained with x-ray.
						Sept. 1947	0.1 mg./K×4		2 months	2 months	Good response to second course. Prompt relief of bone pain. Slow subsidence of fever. Marked subjective improvement. Moderate improvement of cord signs and symptoms.
						11/19/47	0.1 mg./K×4		2 months	1 month	Moderate improvement from third course, definitely less than after previous course.
17	J. DeD.	62	M	1945	X-ray 1945-1946, moderate response of adenopathy. X-ray 1947—back pains unrelieved.	7/8/47	0.1 mg./K×4		6 weeks	None	No response to HN2. Gradual and only slight drop in temperature. No other changes, subjective or objective. Died at home about 6 to 8 weeks after HN2.

TABLE I—Continued

TREATMENT OF MALIGNANT DISEASE

TABLE I—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission		
18	B. E.	22	F	Summer 1946	X-ray June 1947, increased symptoms and signs of superior vena caval obstruction, enlarging mediastinal nodes.	6/23/47	0.1 mg./K×4	10 weeks	> 10 weeks	Marked response to HN2. Decrease of dyspnea after first injection. Subsidence of venacaval obstruction. Marked decrease of adenopathy. Patient asymptomatic.	
19	M. H.	24	F	Feb. 1946	X-ray August 1946, decrease of liver, spleen. Oct. 1946, good response for five months. Asymptomatic until adenopathy April 1947.	6/24/47	0.1 mg./K×4	3 months	2 months	Good response to HN2. Improvement of appetite, feeling of well-being. Diminution of bone pains. Spleen and liver smaller.	
						9/29/47	0.1 mg./K×4 2½ months	2 months		Fair response to second course. Weakness continued but bone pains relieved. Gain of 10 pounds in weight.	
						12/8/47	0.1 mg./K×4 1 month	2 weeks		Shorter period of relief following third course. Bone pains diminished for two weeks. Response definitely less than before.	
						5/26/47	0.1 mg./K×4 2 months	1 month		Moderately good response to HN2. Back pain less severe, pruritus decreased. Nodes slightly smaller, left breast less indurated. Appetite better. Remission very brief.	
20	E. S.	23	F	1941	X-ray—moderate control of symptoms. Developed x-ray burns. X-ray June 1947, very little effect.	7/28/47	0.1 mg./K×4 Teroplerin 5 mg. I.M. daily.	6 weeks	4 weeks	Moderate response to second course. Itching less, nodes smaller, induration reduced. Pleural fluid unchanged. Dyspnea still moderately severe. No further treatment until readmitted in September 1947 for thoracentesis. Hydrothorax rapidly reaccumulating. Pruritus, etc., again marked.	

TABLE I—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission		
21	H. L.	20	F	1945	X-ray 1946, disappearance of nodes, fever, recurrences controlled until last few months.	7/28/47	0.1 mg./K×4 Teroplerin 5 mg. I.M. daily	10 weeks	>10 weeks	Marked symptomatic improvement after HN2. Abdominal and leg pains disappeared. Superficial and abdominal nodes much smaller. Spleen no longer palpable.	
						Oct. 1947	0.1 mg./K×4 Teroplerin	3 months	>3 months	Second course given prophylactically during remission. One week later developed thrombopenia with purpura, and moderate leukopenia but no infection. Symptoms subsided following transfusions. Complete symptomatic remission still maintained in January 1948.	
22	H. H.	24	M	May 1947	X-ray, no response.	7/24/47	0.1 mg./K×4	7 weeks	1½ weeks	Marked improvement after HN2. Compression of bronchus by nodes relieved, pupils became equal, cough and pain reduced. Dyspnea persisted. All symptoms rapidly recurred.	
						9/9/47	0.1 mg./K×4	4 weeks	None	Very slight decrease in symptoms after second course. Progressive downward course terminated in death 10/5/47. Progressive leukocytosis preterminally reached 25,000. No P.M.	
23	D. S.	29	F	Feb. 1946	X-ray 1946, partial response. In 1947 became radioresistant.	9/24/47	0.1 mg./K×4	7 weeks	>7 weeks	Father died of Hodgkin's at 43. Marked response to HN2. Decrease in size of neck mass, axillary nodes, some decrease of hepatosplenomegaly. Feeling of well-being. In two weeks WBC, hemoglobin, platelets dropped sharply. No bleeding. Because of pharyngitis, penicillin given in addition to transfusion. All symptoms subsided.	
24	A. F.	65	M	March 1946	None.	12/8/47	0.1 mg./K×4	4 weeks	3 weeks	Good response to HN2. Marked reduction in size of infraclavicular mass and all nodes. No further radicular pain, felt stronger. Marked drop in WBC to low of 300 with ulcerative pharyngitis and decubitus ulcers. Moderately severe anemia. Platelets low even before HN2. No bleeding. Gradual weakening. Progressive downward course. Died in January 1948, four weeks after HN2. No P.M.	

thrombocytopenia with hemorrhage following two closely spaced courses of HN2; the other death, also due to agranulocytosis, occurred following a single course of HN2 in the standard dosage. Fever, malaise, lymphadenopathy, pulmonary infiltrations, cutaneous infiltrates, and hepato-splenomegaly usually improved with treatment, often dramatically within a few days of institution of a course of therapy. Remissions averaged two months in duration and appeared to be shorter-lived with repeated courses. In two patients who failed to respond to the usual course of HN2, repeated courses at one to three week intervals had striking effects on the disease (Cases 1, 2). However, in Case 1, the toxic effects of the drug proved fatal.

Cases 1 and 2 are reported at length to illustrate points of special interest.

*Case 1.* A 29 year old white housewife first became ill in 1940. At this time she discovered a mass in the right side of her neck which was biopsied and proved to be Hodgkin's disease. She received radiotherapy to the neck and subsequently to the chest with satisfactory improvement. In September 1946, she was readmitted because of lassitude and marked stiffness of the neck, associated with induration of the right supraclavicular area. At this time she received a course of HN2 consisting of 7.5 mg. daily for four consecutive days. Eight days after the treatment she was able to move her head freely. The leukocyte count fell to 2,000 on the thirteenth post-treatment day and then rose to normal. Her general condition improved so that she felt vigorous and strong for the first time in many years. She remained well for two months. In early December 1946, she was readmitted because of recurrent stiffness of the neck, enlargement of the right cervical glands and malaise. She had gained 12 pounds during the two months preceding re-admission.

She appeared well developed and well nourished. There was slight ptosis and exophthalmos of the right eye. The right pupil was constricted. The right supraclavicular fossa was filled with a matted mass of lymph nodes. Smaller nodes were palpable in the left side of the neck, axillae, epitrochlear and inguinal regions. Fluoroscopic examination showed some infiltration at the base of the right lower lobe.

Examination of the blood revealed, hemoglobin 67 per cent; red blood cells, 3.5M/cu. mm.; white blood cells, 6,700/cu. mm.; with 79 per cent segmented polys, 3 per cent non-segmented polys, 12 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophiles; platelets, 120,000; reticulocytes, 1.0 per cent; urine showed a faint trace of albumin; ESR, 60 mm./hour.

Treatment consisted of four doses of 7.7 mg. HN2 intravenously on successive days, by the direct syringe method. As usual, there was nausea and vomiting following each dose. Successive white blood counts on alternate post-treatment days were 3,500, 5,000, 3,700. Eight days following the first course, a second course of treatment was begun. During the first and second days of the second course, white blood counts of 1,800 and 1,950 were reported. On the first day following completion of the second course, the white blood cells were 300, on the second day 200, and the next day 100. At this time, the patient had no complaints. She was given 1,000 c.c. of whole blood. Bleeding from the gums began and she developed a small ulceration on the hard palate. The platelet count was 30,000 and the white blood cells remained at 100. Despite penicillin therapy her temperature began to rise. In an attempt to stimulate leukopoiesis she was given folic acid (pteroyl glutamic acid) and crude liver. Despite numerous transfusions the hemoglobin fell progressively. She developed jaundice, gross hematuria and melena. Shortly thereafter, her left lower quadrant became tender and rigid and a purulent discharge from the rectum was noted. Streptomycin was added to the therapy to control the putative peritonitis; however, her condition continued to deteriorate. On the eleventh day following the second course of HN2, the patient died.

Postmortem examination revealed a small Hodgkin's granuloma in the spleen. There was no visible involvement of the lymph nodes. There was a diffuse necrotizing esophagitis and proctitis. Hemorrhages were prominent in the kidneys, peritoneum, pericardium, gastrointestinal tract, endometrium, lungs and skin. The liver showed only slight fatty changes and congestion.

*Comment:* This case indicates that nitrogen mustard is a potent therapeutic agent in Hodgkin's disease and in adequate dosage may even be curative. However, the curative dose appears to be as destructive to the bone marrow as it is to the granuloma, so that no margin of safety exists. It also illustrates the danger of repeating a course of nitrogen mustard therapy before recovery of the bone marrow. The added insult of a second course when the maximum myelotoxic effect of the first (usually 11 to 15 days following treatment) had not yet been reached, resulted in lethal depression of the bone marrow.

*Case 2.* A 32 year old German accountant was first admitted to The Mount Sinai Hospital June 1946. The patient had been well until August 1943, when he noted increasing fatigue, weakness and loss of weight. On examination a small firm lymph node was found in the left supraclavicular fossa. Biopsy of the node at another hospital revealed Hodgkin's disease. He was then treated with radiotherapy which was effective until 1945, when radiation no longer controlled the disease.

Toward the end of 1945, following radiotherapy, a gland in the right supraclavicular region became fluctuant and spontaneously drained thick yellow pus. Soon after, several glands in the left axilla broke down and began to drain similar material. In addition, he developed pruritic red areas on his extremities and back.

Physical examination revealed a well developed, fairly well nourished white male. There were large matted supraclavicular and cervical nodes. The inguinal, axillary and epitrochlear lymph nodes were bilaterally enlarged. Purulent wounds were noted in the left axilla and right supraclavicular area. Fluctuant masses were located in the left axilla, over the upper thoracic vertebrae, and over the left scapula. The skin of his extremities was covered with numerous circumscribed brown macular lesions. The spleen and liver were not palpable. Ptosis of the right eyelid was present and the right pupil was smaller than the left.

Examination of the blood showed hemoglobin 64 per cent, white blood cells 15,200 with a normal differential count. Roentgen-ray of the chest showed widening of the superior mediastinum. The sedimentation rate was 135 mm./hour. The tuberculin test in concentrations up to 1:100 was negative.

Aspiration of the mass in the left axilla revealed purulent material which was found to be negative for acid fast organisms or fungi. Guinea pig inoculations were negative for tuberculosis. A chronic sinus tract formed following aspiration.

Treatment consisted of a course of sodium arsenite subcutaneously. He received a total of 0.74 gram as a 2 per cent solution over a period of 30 days. During this period there was increasing weakness and anorexia. The hemoglobin fell to 40 per cent and he developed a leukopenia of 4,200. On July 23, 1946, the patient was started on his first course of HN2. He was given 0.1 mg. per kilogram of body weight daily on four consecutive days. By the completion of the course, he experienced disappearance of pruritus. He felt subjectively much improved. There was moderate reduction of the lymphadenopathy and the ulcerations became smaller with diminished drainage. He returned two months later because of recurrence of the original complaints plus pronounced submental adenopathy. A second course of HN2 was begun on September 27, 1946. The effect of therapy was much less dramatic than from the previous course. The submental gland was slightly reduced in size, but the pruritus remained unchanged.



The patient was readmitted two months later because of pains in the back and enlargement of the submental glands. He had received radiotherapy to these areas with no effect in the interval. Pruritus remained unchanged. There was no increased weakness or loss of weight since the last admission. The lower portion of his face was red and swollen. The submental nodes were stony-hard and quite large, and there was a cervical kyphosis. The remainder of the physical examination was essentially the same as at the time of first admission. The hemoglobin was 75 per cent; red blood cells 4.1M/cu. mm.; white blood cells 9,800/cu. mm. with segmented neutrophils 70 per cent, non-segmented neutrophils 12 per cent, lymphocytes 14 per cent, monocytes 4 per cent; platelets 120,000; reticulocytes 1 per cent.

The patient was treated with another course of HN2 0.1 mg. per kilogram daily for four days. Therapy was started on November 20, 1946. There was no remarkable improvement during the next nine days. The leukocytes fell to 4,500, the hemoglobin to 54 per cent. Although the maximum expected leukopenic effect of the HN2 was not yet reached, it was decided to administer another course, since it appeared that the normal dosage recommended was inadequate for this patient. Hence, on December 2, 1946, a fourth course of HN2 was given. Following this course marked improvement was noted: the submental glands diminished greatly in size, pruritus subsided, the pain in the cervical region disappeared, and the patient felt very much improved. On the day of the last dose his white blood cells fell to 900, but the hemoglobin and platelets were relatively normal. For the next three weeks the white cell count ranged between 400 and 1,400. During this period of marked leukopenia there was no evidence of infection. The ulcer in the right supraclavicular area healed completely and the one in the left axilla became clean and presented healthy granulation at the base. The submental glands appeared to be increasing in size again on December 31, 1946, and a fifth course of HN2 was administered. Following this therapy the submental glands again receded. The leukocytes, which had risen to 5000 per cu. mm., fell to 1,500 and the hemoglobin to 48 per cent. The patient was transfused and was discharged one week later markedly improved.

Following discharge the patient was able to return to work for the first time in two years. His remission was maintained until May 1947 with the aid of occasional roentgen-ray therapy to the submental nodes which were now again moderately radio-sensitive. In June 1947 he developed progressive weakness, anemia, increasing lymphadenopathy with edema of both arms and recurrence of the draining wounds in the right supraclavicular area and the left axilla.

He was readmitted in June 1947 for a course of HN2, 10 mg. (0.15 mg. per kg.) daily for four days. There was moderate subjective improvement following this therapy, with decrease of the edema of the arms and regression of the lymphadenopathy. The ulcerations became less purulent, but did not close. The anemia responded to transfusions. About 10 days following an injection into a dorsal vein of the foot with slight extravasation which caused brief, moderate pain, a hemorrhagic bleb 2 to 3 cm. in diameter developed at the site of injection. The bulla broke down superficially, was moderately painful, but healed within one month. Other extravasations of HN2 in this patient (due to the difficulty in finding suitable veins because of multiple thromboses and the edema of the arms) were not followed by any complications.

The remission was not sufficient to permit gainful employment. The patient was admitted to a chronic disease hospital where roentgen-ray and local therapy resulted in healing of the supraclavicular ulceration but did not improve the axillary wound. He became progressively weaker and anemic although not cachectic, and by December 1947 he was able to leave his bed only with difficulty.\*

\* The patient died March 1948.

*Comment:* This patient with Hodgkin's disease with cutaneous infiltrations which had broken down spontaneously forming chronic draining sinuses, had become resistant to radiotherapy, but responded to intensive and repeated HN2 treatment with subsidence of all symptoms and healing of the ulcerations. Remission was maintained for five months. Localized swellings due to Hodgkin's nodes were again radio-sensitive after chemotherapy. As in Case 1, the early repetition of a course of nitrogen mustard (nine days) produced marked leukopenia associated with marked improvement in the granulomata. In this case the leukopenia did not cause symptoms.

*Leukemia:* The results obtained in the treatment of chronic leukemia are summarized in table 2. Of the four cases of lymphatic leukemia, three responded with diminution in lymphadenopathy and hepatosplenomegaly and with subjective improvement but with relatively little change in the blood picture. One patient with lymphosarcoma which had progressed terminally to lymphatic leukemia failed to respond to therapy. The two patients with chronic myelogenous leukemia obtained no improvement. Case 26 is of particular interest because of the development of lymphatic leukemia in a patient who had been demonstrated to suffer from Hodgkin's disease eight years earlier. With the onset of the leukemia the lymphadenopathy and splenomegaly became radio-resistant and progressive severe anemia developed. The response to HN2 was fair, but short-lived, characterized by reduction in hepatosplenomegaly and lymphadenopathy. The hematological picture was not benefited and relapse was prompt.

*Carcinoma:* Fifteen cases of carcinoma were treated with HN2. The cases are summarized in table 3. Only in Cases 35 and 43 did any objective improvement occur. In Case 35 (bronchogenic carcinoma), the metastatic supraclavicular nodes decreased in size and the clouded sensorium cleared. However, death occurred four weeks after treatment, of hemoptysis. Case 43 (Wilms' tumor), showed fleeting regression of the pulmonary metastases.

*Lymphosarcoma:* The eight cases of lymphosarcoma are summarized in table 4. In six cases, brief remissions characterized by reduction in lymphadenopathy were obtained. The remissions averaged four weeks, excluding Case 47 which is reported at length because of the unusually long remission.

\* *Case 47.* A 58 year old white female had noted swelling of the neck five years before admission. A biopsy of a cervical lymph node performed two years later was interpreted as lymphosarcoma. At that time she had developed nodules in the scalp, inguinal, axillary, and mediastinal lymphadenopathy in addition to the cervical involvement. She received roentgen therapy to all of these areas with rapid regression of the nodes.

In December 1946, she was admitted because of a persistent non-productive cough, dyspnea, sweating, weakness, and loss of 10 pounds. Two weeks before admission she had received two roentgen-ray treatments to the mediastinum without apparent improvement. The positive physical findings were enlarged nodes at the angle of the left jaw, multiple, bean-sized nodules fixed to the skin of the scalp, liver enlarged to four fingers'-breadth below the costal margin, spleen palpable one finger's-breadth below the costal margin, enlargement of the right axillary and inguinal nodes,

TABLE II  
Chronic Leukemias

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage		Observation	Remission	
25	L. S.	66	M	1946	X-ray, no response. Stilbamidine, no response.	Sept. 1946	0.1 mg./K $\times$ 4		1 week	None	Lymphosarcoma with terminal lymphatic leukemia. Moribund when therapy begun. No effect from HN2. Died nine days later.
26	M. G.	50	M	1938	X-ray 1938-45, good response. 1946 little effect on adenopathy, enlarging spleen and liver.	11/19/46 12/10/46	0.1 mg./K $\times$ 4 0.1 mg./K $\times$ 4		7 months	2 months	Hodgkin's disease at onset, later becoming chronic lymphatic leukemia. Moderate response to HN2. Marked decrease in hepatosplenomegaly and lymphadenopathy. After two months recurrent anemia treated with varying success by transfusions; edema due to hypoproteinemia. Transferred to chronic disease hospital July 1947, discharged from there in September improved. December 1947 improvement maintained with periodic transfusions.
27	J. G.	47	M	1945	X-ray, one course with moderate response.	Dec. 1946	10 mg. $\times$ 4 (.13 mg./Kg.)		9 months	3 months	Chronic lymphatic leukemia. Moderate improvement after HN2. Decrease of lymphadenopathy. Increase of appetite, well-being. WBC unchanged, slight drop in lymphocytosis. Died August 1947, at home.
28	B. G.	38	F	1944	X-ray, moderate response 1944-47. No effect in 1947. Urethane P.O. and I.V. no effect 1947. Radioactive P, no effect in 1947.	7/28/47	0.1 mg./K $\times$ 4 Teroplerin 5 mg. I.M. daily		1 week	None	Advanced chronic myelogenous leukemia. No response of clinical course or WBC to HN2. Transferred to chronic disease hospital August 1947. Died there in November 1947. P.M. showed leukemia.

TABLE II—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
29	N. D.	38	F	Aug. 1945	X-ray 1945 and 1946, good but very temporary response. Urethane Nov. 1946, splenomegaly reduced. In 1947 no response to urethane or x-ray.	8/5/47	0.1 mg./K×4	4 weeks	1 week	Chronic lymphatic leukemia. Moderate response to HN2. Proptosis of right eye decreased. Slight decrease of size of nodes. Disappearance of papilledema O.D. with marked improvement in vision. Subjectively improved. Ascites recurred, required tapping. Died at home September 1947 approximately three weeks after discharge.
30	G. W.	43	M	1944	X-ray 1945-1946, good response. Urethane Oct. 1946, slight response. P32 1947, no noticeable effect.	9/13/47	0.1 mg./K×4	3 weeks	None	Chronic myelogenous leukemia. No response to HN2. Died at home October 1947, approximately two weeks after discharge.

TABLE III  
Carcinomas

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
31	S. M.	60	M	1946	None	11/27/46 12/7/46	10 mg./K×4 10 mg./K×4 (.17 mg./Kg.)	6 weeks	None	Liver biopsy, small round cell CA probably metastatic from lung. Some relief of cough and abdominal discomfort following HN2. No other improvement. Marked leukopenia and moderate thrombopenia following second course.
32	J. DeB.	41	F	Sept. 1946	None	Jan. 1947	0.1 mg./K×4	1 month	None	Biopsy, infiltrating mature squamous cell CA of the lung. No response to HN2. Gradual downward course, ending in death 2/15/47 at chronic disease hospital. No P.M.
33	P. R.	51	M	Aug. 1946	None	Dec. 1946	0.1 mg./K×4	1 month	None	Squamous cell CA of lung, inoperable. No response to HN2.
34	P. S.	51	F	Aug. 1946	None	11/26/46 12/19/46	0.1 mg./K×4 0.1 mg./K×4	2 months	None	Squamous cell CA of lung with pleural metastases. No response of fever, effusions, masses to HN2.
35	A. L.	47	M	Oct. 1946	X-ray, no response.	Nov. 1946	0.1 mg./K×4	4 weeks	4 weeks	Bronchogenic adenocarcinoma. Supraclavicular nodes softer and smaller. Node biopsy showed necrosis after HN2. Sensorium clearer. Died at home due to hemoptysis two weeks after discharge.
36	M. E.	52	M	Jan. 1946	Lobectomy RLL, partial lobectomy RML, RUL.	Jan. 1947	0.1 mg./K×4	3 weeks	None	Adenocarcinoma of lung, metastases to nodes and skin. No response to HN2.
37	S. E.	43	F	Jan. 1945	X-ray, minimal response.	Dec. 1946	0.1 mg./K×4	2 weeks	None	Bronchogenic CA, biopsied at exploratory. No response to HN2. Died of congestive failure (rheumatic heart disease) two weeks after HN2.
38	R. W.	66	F	June 1946	None	1/5/47	0.1 mg./K×4	4 weeks	None	Bronchogenic CA—inoperable. No response to HN2.
39	M. S.	38	F	Dec. 1945	X-ray, minimal response.	Nov. 1946	0.1 mg./K×4	3 months	None	Squamous cell CA of lung. No response to HN2. Slowly deteriorating.

TABLE III—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage		Observation	Remission	
40	A. S.	49	F	June 1947	None	7/28/47	0.1 mg./K×4 Teroplerin 5 mg. I.M. daily.		2 weeks	None	Immature squamous cell CA of lung. No response to HN2. Transferred to chronic disease hospital July 1947. Deteriorating steadily.
41	J. S.	47	F	1943	X-ray, A. C. S., no response.	10/28/46	0.1 mg./Kg. ×4		3 weeks	None	Scirrhus carcinoma of the breast with metastases to both breasts, bones, liver, peritoneum. No response to HN2. Died three weeks later. Diagnosis confirmed at P.M.
42	D. W.	4	F	1946	Nephrectomy and post operative irradiation followed by appearance of single metastasis in lung.	3/12/47	0.1 mg./K×5		3 months	None	Wilms' tumor. Metastasis to lung in February 1947. No response to HN2 or to radiotherapy. Pneumonectomy May 1947 with uneventful convalescence.
43	E. K.	2½	M	Feb. 1947	X-ray March 1947 followed by excision of kidney, appearance of pulmonary metastases.	May 1947	0.1 mg./K×4		4 weeks	1 week	Wilms' tumor. Marked resolution of pulmonary metastases after HN2, with recurrence in two weeks. Tumor nodules appeared in abdomen during and immediately following HN2.
44	R. A.	30	F	1946	Radioactive I early 1947 with no effect except decrease of mass in neck. X-ray to spine with relief of pain.	6/25/47	0.1 mg./K×4		3 weeks	None	Anaplastic metastatic CA, 1° site undetermined. No response to HN2. Transferred in deteriorating state to chronic disease hospital in July 1947.
45	J. I.	40	M	1946	None	7/18/47	0.1 mg./K×4		8 weeks	None	Metastatic melanocarcinoma. Very slight and temporary relief of bone pains after HN2. Deteriorated steadily, died October 1947. P.M. showed generalized metastases. Primary not found.



TABLE IV—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
50	B. G.	53	M	April 1946	X-ray for one year with moderate response.	5/2/47	0.1 mg./K×4	2 months	6 weeks	Prompt excellent response to HN2 with decrease of nodes, feeling of well-being and improved appetite. Maintained improvement after discharge.
						7/11/47	0.1 mg./K×4	10 days	> 10 days	Moderate response to HN2. Marked decrease in bone pain, gradual decrease of edema, less change in size of nodes. Discharged to V. A. hospital for chronic care.
51	E. H.	63	F	April 1947	None	8/12/47	0.1 mg./K×4 Teroplerin 5 mg. I.M. daily.	4 weeks	1 week	Fair response to HN2. Abdominal mass no longer felt. Axillary node smaller. Slight brief subjective improvement. Progressive deterioration until death in September 1947. No P.M.
52	S. H.	53	F	Nov. 1946	None	2/19/47	0.1 mg./K×4	6 months	2 weeks	Good response to HN2. Nodes much smaller. Recurrence of weakness, nausea, vomiting, fever treated by x-ray with excellent response in May 1947. Since then, remained fairly well. Last seen in August 1947, with improvement maintained.
53	G. H.	67	M	Dec. 1943	X-ray 1944, moderate response. Paracentesis for chylous ascites with no recurrence. X-ray 1947, little effect.	10/22/47	0.1 mg./K×4	10 weeks	None	No effect of HN2. Chylous pleural fluid and ascites reaccumulated. WBC and platelets remained at low figure of pretreatment levels. Edema, weakness, anemia persisted. Bed-ridden at home, gradually deteriorating in January 1948.



fading ecchymoses on the lower legs. Chest roentgenogram revealed a large mediastinal mass. The blood picture revealed hemoglobin 51 per cent, white blood cells 3,150, platelets 20,000. She was treated with a course of four injections of HN2, 0.1 mg. per kilogram, with rapid, well-marked shrinkage of the axillary nodes, liver, mediastinal mass and scalp nodules. The leukopenia and thrombocytopenia were not aggravated by therapy during the two week period of hospital observation.

During the next 10 months she regained her appetite, weight and strength. In October 1947 she began to complain of back pain, for which she received one roentgen-ray treatment without effect. During the next two months she developed intermittent fever, sweating, anorexia, weakness, and mild cough. She was readmitted in November 1947 for a second course of HN2. Physical examination disclosed an egg-sized node at the angle of the left jaw, tenderness in both upper quadrants, liver and spleen each 3 fingers'-breadth below the costal margin, a firm grapefruit sized mass in the mid-lower abdomen, and inguinal adenopathy. There were marked varicosities of the legs with moderate edema. Tenderness was elicited over the twelfth dorsal vertebra. Hemoglobin was 75 per cent, white blood cells 6,350/cu. mm., platelets 180,000. The scalp nodules had recurred, but had disappeared again following roentgen-ray irradiation.

A second course of HN2 was administered with improvement in appetite, subsidence of back pain, diminution in size of lymph nodes and slight decrease in the size of the mediastinal mass. During the one month period of observation the abdominal findings did not change significantly.

*Comment:* The 10 month period of remission following the first course of HN2 represents an unusually favorable response in this disease.

*Miscellaneous:* Table 5 summarizes 11 cases of miscellaneous diseases. Of the three cases of reticulum cell sarcoma, one (Case 58) responded to HN2 therapy with a prolonged remission (still maintained at end of five month observation period) characterized by reduction of hepatosplenomegaly, subsidence of fever and icterus. The other two patients (Cases 59, 60) experienced exceedingly brief improvement. One patient with widespread spindle cell sarcoma of the bones (Case 57) and one with Boeck's sarcoid (Case 62) were not benefited by HN2. Two patients with undiagnosed tumors, thought to be mediastinal (Case 64) and retroperitoneal (Case 63) lymphomata were treated. The former experienced marked relief of venous and bronchial obstruction. The latter was briefly relieved of abdominal pain associated with slight reduction in the size of the mass. One patient (Case 56) with lymphosarcoma proved by inguinal lymph node dissection in 1941, developed generalized lymphadenopathy, fever, and splenomegaly in 1946. He received roentgen-ray therapy and then HN2 without benefit. Postmortem examination revealed miliary tuberculosis without evidence of lymphosarcoma. The impression was that surgical dissection had eradicated the localized lymphosarcoma and that the subsequent tuberculosis, which mimicked generalized lymphosarcoma, was not responsive to HN2.

Of the two cases of mycosis fungoides, one (Case 55) responded with marked objective and subjective improvement after one course of 10 mg. (0.17 mg. per kilogram) HN2 daily for four days. The improvement of the skin lesions and the reduction of lymphadenopathy and splenomegaly

TABLE V  
Miscellaneous Diseases

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2			Post HN2 Period of		Comments
						Date	Dosage		Observation	Remission	
54	S. M.	74	F	1941	Local therapy, no effect.	2/16/47	0.1 mg./K×4		1 month	None	Mycosis fungoides. No response to HN2. Slight relief of itching for only one week. No effect on skin lesions.
55	H. G.	55	F	1941	Local therapy—no effect. X-ray—partial control over three years up to last five months.	1/6/47	10 mg.×4 (.17 mg./Kg.)		5½ months	3 months	Mycosis fungoides. Moderate response to HN2. Definite improvement of skin lesions with disappearance of nodules, reduction of erythema and induration, of lymphadenopathy, and of splenomegaly. Partial relief of itching. Returned to hospital 4/23/47, with exacerbation of skin lesions and infiltration in mouth. Radiotherapy with good response.
56	M. M.	24	M	1941 1946	X-ray 1941 for inguinal adenopathy (lymphosarcoma diagnosed by biopsy)—nodes disappeared. X-ray 1946—47 for recurrence involving prostate, seminal vesicles, axilla—no effect.	1/7/47	10 mg.×4 (.16 mg./Kg.)		6 weeks	None	Lymphosarcoma proved by inguinal node biopsy in 1941. Treated with x-ray. Recurrence adenopathy, rectal masses, splenomegaly in 1946 not responsive to x-ray or HN2. Transient purpura and thrombopenia followed course of HN2. Patient died Feb. 1947. P.M. findings: caseous tuberculosis with hematogenous dissemination. No evidence of lymphosarcoma.
57	F. F.	38	F	1945	X-ray early 1947—minimal relief of bone pains.	5/14/47	0.1 mg./K×4		4 weeks	None	Pleomorphic spindle cell sarcoma of bone, rapidly growing. No response to HN2 or x-ray. Died soon after treatment. P.M. findings: Spindle cell sarcoma of bones and hilar nodes and SBE on rheumatic valves.

TABLE V—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
58	L. S.	49	F	1946	X-ray—no effect.	March 1947	0.05 mg./K×2 0.1 mg./K×3	5 months	>5 months	Reticulum cell sarcoma. Half dose given because of leukopenia before treatment. Hepatosplenomegaly, icterus, fever subsided. WBC unchanged. Still well in August 1947.
59	M. F.	56	M	1947	None	August 1947	0.1 mg./K×4	1 week	None	Reticulum cell sarcoma. Remission of fever for three days. Spleen shrunk from five fingers below costal margin to costal margin. Died one week after treatment. P.M. findings: reticulum cell sarcoma involving both adrenals.
60	F. T.	42	M	July 1947	X-ray August 1947—partial but very temporary response.	11/17/47	10 mg.×4 (.15 mg./K)	5 weeks	One week	Reticulum cell sarcoma, rapidly growing. Slight temporary response to HN2. Neck mass decreased in size for one week. Recurrence together with dorsolumbar back pain partly controlled by x-ray therapy.
61	L. K.	42	F	1938	None	Oct. 1946	0.1 mg./K×4	15 months	8 months	Non-leukemic myelosis. Very good response to HN2. Splenomegaly considerably reduced. Hepatosplenomegaly slightly diminished. Hematological picture returned to normal, but rose gradually during succeeding 15 months. Splenomegaly returned to pretreatment level 15 months after therapy. See case report.
62	J. W.	39	M	1946	None	12/2/47	0.1 mg./K×4	2 weeks	None	Boeck's sarcoid. Diagnosis based on clinical and x-ray picture, and positive sarcoid skin test. No objective changes after HN2, but subjectively dyspnea was less.

TABLE V—Continued

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of IIN2			Post HN2 Period of		Comments
						Date	Dosage		Observation	Remission	
63	H. K.	52	M	1947	None	April 1947	0.1 mg./K×4	3½ months	3 months	Lymphoblastoma—no biopsy possible at time of exploratory which demonstrated retroperitoneal mass. General though incomplete improvement following HN2. Able to work. Abdominal mass remained palpable.	
				8/16/47			0.1 mg./K×4	4 weeks	1 week	Recurrent pain in RUQ relieved promptly by HN2. Liver and LUQ mass decreased moderately in size. Fever, anorexia, dyspnea occurred 2½ weeks after HN2.	
				9/21/47			0.1 mg./K×4	1 month	None	Severe anorexia, weakness, anemia, with melena. Progressive downward course unaffected by HN2. Died one month later. No P.M.	
				10/27/47			0.1 mg./K×4	4 weeks	2 weeks	Diff. diagnosis between bronchogenic carcinoma and lymphoma cannot be made. Excellent response to HN2. Able to lie flat for first time since onset. Superior vena caval obstruction and edema cleared but all recurred in two weeks. Chylothorax persisted.	
64	H. D.	52	M	Sept. 1947	X-ray 1947—no improvement.	12/3/47	0.1 mg./K×4	2 weeks	>2 weeks	Dyspnea and orthopnea cleared again, after HN2.	

were maintained for three months. The other patient failed to respond to 0.1 mg. per kilogram daily for four days.

The one patient with non-leukemic myelosis (Case 61) is reported at length.

*Case 61.* A 42 year old white female was admitted to the hospital on September 28, 1946. Eight years prior to her admission the patient had noticed a large area of ecchymosis over the right leg which was apparently unrelated to trauma. Since that time she had suffered spontaneous ecchymoses over various parts of the body which slowly disappeared without symptoms. For the past six years she noted progressive enlargement of her abdomen and experienced gradually increasing fatigability.

The morning of the day of admission she suddenly developed agonizing, sharp pain in her right upper quadrant which radiated to the back and which was associated with a feeling of faintness. No abnormal genito-urinary history could be elicited.

Physical examination at the time of admission revealed a well developed and well nourished adult female in no acute distress. The skin showed an area of fading purpura over the left thigh with fine varicosities in this region. There were areas of increased pigmentation over the sternum and over the ankles. The abdomen was protuberant and the liver was enlarged to three fingers below the right costal margin. It felt smooth and firm. The spleen filled the left half of the abdomen reaching down to the iliac crest and was firm, smooth and non-tender. The rest of the physical examination was normal.

On admission her hemoglobin was found to be 70 per cent; white blood cell count 26,000, with 73 per cent polymorphonuclear cells, 18 per cent stabs, 5 per cent lymphocytes, 1 per cent basophiles and 3 per cent myelocytes. The platelet count was 320,000. The urine showed 1 plus albumin, 3 to 4 white blood cells and an occasional red blood cell per high power field. Sedimentation rate was 17 mm. in one hour. Stool guaiac was negative, phenolsulphonephthalein excretion 55 per cent in 2 hours, uric acid 10.8 mg./100 c.c., and other blood chemistries were within normal limits. Prothrombin index was 100 per cent of normal; urine culture was negative; hematocrit 40 per cent; blood volume 88 c.c. per kilogram. Retrograde pyelography revealed no abnormalities. Esophagogram and chest roentgen-ray were negative. Examination of the long bones was reported as showing changes in the upper ends of the femora, tibiae, and humeri, suggestive of myelofibrosis. The sternal myelogram was normal.

Investigation of the cause of her acute pain prior to admission was without results. Because the enlarged spleen was mechanically symptomatic it was decided to try HN2 therapy, although the disease was considered to be non-leukemic. For four successive mornings the patient received 5.8 mg. (0.1 mg. per kilogram) of HN2 intravenously. Following the first injection she became severely nauseated and vomited over a period of four hours, but the other three injections were not followed by nausea or vomiting. Three days after the last injection the white blood count had fallen to 14,500 and the next day the count was 8,500 with no myeloblasts nor myelocytes seen in the peripheral smear. The count continued to fall to a low of 2,000 on the twelfth day after treatment, associated with a fall in the percentage of neutrophils from 84 per cent to 60 per cent and a rise in the lymphocytes from 4 per cent to 19 per cent. Subsequently, the white blood count rose to normal; the neutrophils increased to 71 per cent and the lymphocytes fell to 10 per cent. At the time of discharge, three weeks after treatment the white count was 7,900 with no myeloblasts or myelocytes in the peripheral blood. The change in size of the spleen was no less dramatic. On the day following her last injection there was noted a slight but definite diminution in its size. The patient too, remarked that her abdomen felt smaller and lighter to her. The spleen continued to shrink rapidly in size for

about two weeks at which time it was about one-half its previous size. Study of the bone marrow, one week after treatment, revealed no significant changes from that prior to treatment. Concomitant with the reduction in the size of the spleen there was marked symptomatic improvement noted by the patient. She no longer was aware of her enlarged abdomen nor dragging sensation, and her strength and endurance increased. When seen six months later, there had been no change in the size of the liver (four fingers'-breadth below the costal margin) and the spleen had remained at about half its pre-treatment size. Her appetite was good and there had occurred an eight pound gain in weight associated with a persistent feeling of well-being. The blood revealed hemoglobin 78 per cent, red blood cells 4.0M/cu. mm.; white blood cells 12,200/cu. mm. with segmented neutrophils 78 per cent, stabs 15 per cent, lymphocytes 5 per cent, monocytes 1 per cent, eosinophiles 1 per cent. Nine months after treatment, she experienced a second episode of right upper quadrant pain, which subsided spontaneously after one day, as on the first admission. At this time, her spleen was noted to be slowly enlarging. The white blood cell count was 15,000/cu. mm. She was last seen in January 1948. At that time she was steadily employed and had no complaints. However, the spleen had returned to approximately pre-treatment size. The hemoglobin was 59 per cent, red blood cells 3.8M/cu. mm., white blood cells 15,000/cu. mm. with 1 per cent metamyelocytes, 28 per cent non-segmented polymorphonuclear neutrophils, 59 per cent polymorphonuclear neutrophils, 7 per cent lymphocytes, 4 per cent monocytes, 1 per cent basophiles, 3 per cent eosinophiles, 1 normoblast/100 white blood cells, 180,000 platelets.

*Comment:* This patient with chronic non-leukemic myelosis (myelofibrosis) with marked splenomegaly responded to HN2 therapy with dramatic decrease in the splenomegaly and with return of the blood picture to normal. Remission was maintained for seven months. However, during the next eight months, the spleen returned to its pre-treatment size and moderate leukocytosis recurred.

## DISCUSSION

Our results are in general agreement with those of other investigators. Favorable results comparable to those obtained with radiotherapy followed the HN2 treatment of most cases of Hodgkin's disease. Fever, when present, subsided dramatically by the third day of therapy. A sense of well-being and regression of the lymphadenopathy were usually noted during the first post-treatment week, while the hepato-splenomegaly receded during the second week. Marked reduction in the size of the spleen, contrary to earlier reports, was common. In a few cases (Cases 4, 10, 16, 20) the pain due to bone lesions responded satisfactorily. One patient (Case 2), who had become roentgen-ray resistant, responded to nitrogen mustard and was subsequently sensitive to radiotherapy again. Relapses occurred in all cases in a few days to 10 months. In most cases, remissions became progressively shorter with successive courses of HN2. Chronic lymphatic leukemia, lymphosarcoma, mycosis fungoides and reticulum cell sarcoma showed variable responses. Carcinomas were uniformly unresponsive except for one bronchogenic adenocarcinoma and one Wilms' tumor (Cases 35, 43). One patient with chronic non-leukemic myelosis was dramatically benefited

with diminution in the size of the spleen and restoration of the normal blood picture (Case 61).

Post-treatment biopsies usually revealed necrobiosis and necrosis; but since these are frequent findings even in untreated malignancies, their significance cannot be evaluated.

No cures were observed. However, in one patient with proved generalized Hodgkin's disease, only one small splenic granuloma with degenerative changes could be found at postmortem examination. Death in this case was due to agranulocytosis and thrombocytopenia secondary to excessive therapy. Since almost complete suppression of the granulomatous disease was obtained, this patient illustrates the desirability of treating with the maximum tolerated dosage. Furthermore, the evidence suggests that even refractory cases respond with longer remissions to closely spaced multiple courses. However, while early re-treatment appears advantageous, a second course within two weeks is definitely hazardous. At this time the maximum myelotoxic effect has not yet been attained or has only just been reached. The regenerating marrow, with its fewer, mitotically more active blasts, is apparently more sensitive to the reagent, so that a dramatic fall in the white blood count occurs on the second to fourth day of re-treatment. We have found that approximately one and one-half to two times the recommended standard dose of 0.1 mg. per kilogram produced no more frequent or severe leukopenia than the standard dose. However, we were unable to demonstrate any clear cut advantage in the larger dosage. Both dosage schedules resulted in unpredictable myelotoxic effects. A fatal outcome due to agranulocytosis was observed in a patient who received a single standard course (Case 24), whereas some patients who received larger doses showed only minimal leukopenia. It is our opinion that the recommended schedule of therapy might be advantageously revised to provide for an initial series of closely spaced courses for maximal therapeutic effect, perhaps to be followed by regularly spaced maintenance doses.

The toxic reactions noted by us were the same as those previously reported. They appear to be unrelated to the rate of injection. We fortunately had no significant extravascular infiltrations, but mild thrombophlebitis was common. Nausea and vomiting occurred in almost all cases, but was often milder with successive injections. No appreciable relief of this symptom was obtained with pyridoxine, atropine, teropterin or sedation. The numerous visceral function tests performed by us revealed no changes attributable to the HN2 therapy except for the hematopoietic response. Lymphopenia usually occurred between the third day of treatment and the second post-treatment day. Leukopenia below 3,000 developed in almost every case with the minimum white cell count on the third to twenty-fifth post-treatment day (average 11 days); infection was rare even with counts below 1,000. There were only four cases of infection (pharyngitis), all among the Hodgkin's cases. Anemia, secondary to treatment, was noted only twice (Cases 23, 48), and thrombocytopenia was noted seven

times, with bleeding in four. A significant change in the myelogram was noted only once (Case 48) characterized by marked depression in erythropoiesis associated with anemia, but total nucleated counts were not done. The hematotoxic effect was entirely unpredictable, nor was its severity related to the response of the primary disease. Teroplerin had no effect in preventing the myelotoxic effect or in hastening recovery. The effect of combined Teroplerin and HN2 therapy on the primary disease was indistinguishable from that of HN2 therapy alone (eight cases).

We are of the opinion that methyl bis ( $\beta$ -chloroethyl) amine (HN2) is of value in the treatment of Hodgkin's disease, occasionally in lymphosarcoma and mycosis fungoides, and probably in non-leukemic myelosis. It appears to be of no value in the treatment of carcinomas. We believe that in certain instances the nitrogen mustards have advantages over their physical counter-part, roentgen-ray. In cases of wide-spread or inaccessible lymphomatous lesions, where roentgen therapy is not feasible, the drug finds particular application. Fever due to lymphomata responds much more regularly and dramatically to chemotherapy. In moribund cases, the more rapid and occasionally dramatic effect of HN2 is advantageous. Constrictive lesions of the great vessels or the spinal cord often respond more rapidly to the chemical agent than to roentgen-rays. The initial swelling of tumor tissue often seen following roentgen-ray therapy has not been observed with HN2. For the treatment of readily accessible or localized lesions, we continue to regard radiotherapy as the treatment of choice. As with roentgen-ray, we have noted that response to HN2 may be used as a therapeutic test in the differential diagnosis of lymphomatous diseases (cf. therapeutic failure in Case 56 (miliary tuberculosis) and response in Case 59 (reticulum cell sarcoma at post mortem)).

#### SUMMARY

1. Sixty-four patients with a variety of malignant diseases were treated with methyl bis ( $\beta$ -chloroethyl) amine hydrochloride.

2. Brief remissions were obtained in 20 of 24 cases of Hodgkin's disease including several who had become roentgen-ray resistant. Carcinomas were uniformly unresponsive (with two minor exceptions). Reticulum cell sarcoma and chronic lymphatic leukemia were only fleetingly benefited or failed to respond at all. One patient with chronic non-leukemic myelosis with splenomegaly and myelofibrosis improved dramatically. Lymphosarcoma and mycosis fungoides responded variably, but the results were usually poor. Chronic myelogenous leukemia did not respond.

3. Toxic effects similar to those previously described were noted.

4. The advantages and hazards of larger doses and repeated courses at short intervals are discussed.

5. The relative merits of roentgen-ray and nitrogen mustard therapy are summarized.



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# THE PHYSIOLOGICAL AND BIOCHEMICAL BASIS FOR THE USE OF VITAMIN E IN CARDIO- VASCULAR DISEASE \*

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VITAMIN E first came to medical notice as a preservative of precarious pregnancies, whether habitual<sup>1</sup> or threatened abortions.<sup>2,3</sup> Its rôle in the maintenance of normal gestation was later emphasized with respect to premature placental detachment<sup>4</sup> and non-eclamptic toxemias.<sup>5</sup> Certain uses in gynecology, such as in the menopause,<sup>6,7</sup> in senile vulvitis<sup>8,9,10</sup> and even in male sterility,<sup>11</sup> were also reported. But, fundamentally, for the first 25 years of its existence it did justify the appellation of "fertility vitamin" which now seems so misleading.

That this vitamin played a much more significant rôle than this "bit part" could have been inferred even long before 1945 from the studies of Madsen, Mason, Hickman and Harris, Houchin and Mattill and others. For example, the musculature proved to be a major site of involvement in the E-deficient hamster, rabbit or guinea pig, the vascular system in the monkey, and the heart in the monkey, rabbit and cow. "The association of vitamin E with the reproductive process, therefore, is largely due to a laboratory accident, and it is almost time, 25 years later, that we broke the unfortunate linkage produced in most medical minds by those first aborting rats."<sup>12</sup> For vitamin E, to quote Hickman and Harris, is "the most versatile and active of all the vitamins."

Seen through the eyes of the biochemist, vitamin E plays a still larger rôle. It is even an anomaly among fat-soluble vitamins, since it "behaves as a water-soluble vitamin that requires a lipid carrier for transport." It is one of the two great stabilizers of the blood during the digestive journey." It is the balance-wheel of the oil-soluble vitamins and the unsaturated fats. It is implicated in phosphorus metabolism—and its effects extend to the utilization of oxygen and the aging of the whole animal organism."<sup>13</sup> It is both oxidant and anti-oxidant. Indeed a more versatile participant in the bodily mechanism could scarcely be imagined, and it is not too surprising, therefore, that drastic changes develop in many tissues and systems in the face of E-poverty.

As internists in general, and cardiologists in particular, may not be fully aware of the more relevant animal experimentation in this field, it can be briefly summarized here in order to illustrate the broad basis on which our studies now stand, and to encourage perusal of the original papers, notably Govier's.

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Madsen<sup>14</sup> first showed that myocardial scarring developed in rats after prolonged deprivation of vitamin E. Mason and Emmels<sup>15</sup> confirmed this, and observed gross cardiac enlargement in a large series of such animals coming to autopsy. The pigment found in their heart muscles seemed to be identical with that found in brown atrophy in the senile human heart. Gatz and Houchin<sup>16</sup> reported analogous findings in the hearts of E-deficient rabbits, an observation lately confirmed by Bragdon.<sup>17</sup>

Electrocardiographic changes similar to those seen in failing hearts in man have been found in E-low rats by Butturini,<sup>18</sup> and by Martin and Faust<sup>19</sup> in rats and rabbits, but not by Ensor<sup>20</sup> in rats. Mason and Telford<sup>21</sup> report that E-deficient monkey hearts showed myocardial fibrotic areas, although in the macaque vascular degenerations seemed to preponderate. Holman<sup>22</sup> has also done interesting work relating vitamin E to vascular lesions in dogs.

The study of Gullickson and Calverly<sup>23</sup> on the hearts of E-deficient cattle bids fair to become a veterinary classic. We understand that these authors possess a great wealth of unpublished material, accumulated from a study of over 10 years' duration. Fundamentally, their observations pointed clearly to E-deprivation in cattle producing death from heart failure, with electrocardiographic changes resembling those seen in myocardial damage in man, and with postmortem myocardial foci suggestive of those seen in rheumatic affections in the human.

An interesting piece of clinical work in the veterinary field was reported by Lambert.<sup>24</sup> Dogs and cats in undoubted heart failure were restored to good functional efficiency on the administration of vitamin E. This clinical work on dogs and cats has been widely substantiated, we might add, and some of these veterinary cases have come to our personal attention.

This extensive animal work, some of it antedating our own clinical observations, lays a strong a priori basis for the relationship of vitamin E to cardiovascular lesions in man, should humans ever be suspected of E-deficiency.

That the average American diet is often inadequate in available vitamin E has been clearly demonstrated by the careful calculations of Harris et al.<sup>25</sup> and by Quaife and Harris.<sup>26</sup> A very good exposition of how this can develop is given by Hickman<sup>27</sup> in a recent letter to the *Lancet*. It would appear that the average American industrial worker gets only from 10 to 90 per cent of his daily requirement of tocopherols. This deficiency is further aggravated by large intakes of milk, butter, white bread and root vegetables, as well as of rancid and unsaturated fats. This deficiency is at least as marked in the upper economic strata as in those less fortunate. The assimilation of vitamin E in healthy persons is less than 50 per cent, and in deficient persons may be much less.

Govier et al.<sup>28</sup> as well as Spaulding and Graham,<sup>29</sup> have carried out extensive studies on the enzyme systems of heart muscle. "Anoxia in heart muscle is the accepted cause of congestive failure." It is known that in states

of cardiac anoxia coenzyme I is broken down, although it is needed for the proper metabolism of lactate, the preferred substrate of heart muscle. Now alpha tocopherol both inhibits coenzyme I nucleotidase and can also inhibit succinoxidase and lactic dehydrogenase. Govier suggests that if heart muscle in congestive failure is E-deficient, as its low creatine content resembling that of other E-deficient muscles might suggest, this deficiency would permit coenzyme I nucleotidase to act in a system already anoxic and thus produce that breakdown of coenzyme I which is known to occur in such heart muscle. This breakdown of coenzyme I would seriously derange heart metabolism. It is noteworthy that digitoxin seems to prevent such breakdown of coenzyme I in E-deficient muscle, and that alphetocopherol also seems able to prevent its destruction, by inhibiting coenzyme I nucleotidase. Govier has more recently concluded, we understand, that the somewhat similar results in these enzyme systems are accomplished differently, the one substance increasing production of coenzyme I and the other retarding its destruction.

Our own observations<sup>30-33</sup> on the value of alpha tocopherol as a therapeutic agent in various types of cardiac and renal disease we do not propose to review here, as they are rapidly becoming too extensive for convenient summary. Our electrocardiographic studies should soon appear.<sup>34, 35</sup> We ought to emphasize, however, that our conclusions were originally pragmatic, not based on any of this animal work or dietary analysis, and stand or fall by themselves as clinical observations.

Vitamin E therapy in our hands is not substitution therapy, but a form of chemotherapy. This is a point that deserves emphasis. The doses we use are larger than nutritional studies would demand, but usually smaller dosage is ineffectual. We think of alpha tocopherol as a chemical compound which also happens to be a food constituent, but whose dosage level in established cardiac disease is not closely related to that coincidence. The analogy to the modern use of vitamin D is suggestive. A small dosage of E gives but little hint of what it can accomplish in massive dosage. What could be hoped for from a small and more nearly physiological dose administered over a period of years is, of course, quite a different consideration and one on which we have little evidence as yet, although it is a problem of vital importance.

## SUMMARY

The physiological and biochemical evidence supporting the use of vitamin E in cardiovascular disease is reviewed.

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# HEPATITIS AMONG AMERICAN OCCUPATION TROOPS IN GERMANY: A FOLLOW-UP STUDY WITH PARTICULAR REFERENCE TO INTERIM ALCOHOL AND PHYSICAL ACTIVITY \*

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THE relationship of alcoholism to the development of cirrhosis of the liver has been a subject of investigation and controversy for many years.<sup>1-8</sup> More recently, the relation of antecedent attacks of acute infectious hepatitis to the later development of cirrhosis and the immediate progression of some cases of chronic hepatitis into cirrhosis has received attention.<sup>9, 10, 11</sup> Because of the obscurity of this relationship, and the suspicion that the possible hepatotoxic effect of alcohol might be enhanced in an already damaged liver, and since it has been frequently stated in the literature that alcohol may be a factor in precipitating relapses, most physicians have forbidden alcohol to their patients for some months following recovery from the acute disease. As the clinical picture of the present endemic, sporadic, but widespread hepatitis seen among American troops in Germany differs in several respects from the *epidemic* infectious hepatitis studied by Barker, Capps and Allen<sup>12, 13</sup> during the war in the Mediterranean, it was thought worthwhile to study the incidence of residuals in patients who had had hepatitis six months to one year before with particular reference to their alcoholic intake and physical activity in the intervening period. An opportunity to study this situation presented itself at the Hepatitis Center maintained by the Medical Department of the U. S. Army European Command in Germany. Shortly after its inception, the Hepatitis Center was forced by military necessity to discharge some patients with laboratory and clinical evidence of incomplete recovery from acute hepatitis. This provided an opportunity to study the effects of alcohol and exercise during convalescence as well as the period immediately following apparent cure. An attempt was therefore made to recall for further study all patients who had been hospitalized at the Hepatitis Center and discharged within a period of six months to one year. Observations made on these patients furnished the basis of this report, and

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appear to indicate that large amounts of alcohol or strenuous activity during the period of convalescence played no more significant a rôle in the incidence of residuals than total abstinence or a sedentary life in the *particular* group studied.

At the present time, it is impossible to distinguish on clinical grounds between the naturally occurring infectious hepatitis (IH) and homologous serum hepatitis (SH). Certain features of the hepatitis, both clinical and epidemiological, suggest that both forms are present among the American troops in Germany, with perhaps a greater number of the latter. A third possibility, that of naturally occurring infectious hepatitis (IH) being transmitted parenterally by inoculation is also suggested. For the purposes of this report, however, these etiological distinctions have had to be ignored as no precise separation is possible. As toxic hepatitis (usually due to carbon tetrachloride) is not uncommon among the American troops, every effort has been made to exclude this. Weil's disease has not been a problem among American troops in Germany, and leptospiral agglutinations and complement fixation on both acute and convalescent sera have been performed on all suspicious cases as well as in a check survey of the patients in the Hepatitis Center.\* These have all been negative.

#### MATERIALS AND METHODS

Without using criteria for selection other than their availability within the theater, soldiers who had been previously hospitalized for either infectious hepatitis or serum hepatitis and who had been discharged from the Hepatitis Center six months to one year before, were asked to return for follow-up studies.

Of the 652 patients who had been discharged during the period, 114 patients reported for this type of follow-up examination. Although the number of relapses in those patients who had returned to the United States cannot be ascertained, only two patients were readmitted to the Hepatitis Center with true relapses (manifested by either clinical and/or abnormal laboratory findings). One of these was known to be an alcoholic about 42 years old; the other was classified as a moderate drinker. Both eventually recovered. Their interval alcoholism is not known.

The group as a whole was representative in age of the soldiers of the U. S. Army of Occupation, ranging from 19 to 36, with an average age of 22.7. The character of illness sustained by these men had not been remarkable in severity. The average length of hospitalization initially had been 62.1 days. The great majority of these men had been in good physical condition prior to the acquisition of the hepatitis. Their diets had been adequate, even ample, both prior to the onset of the disease and during the

\* These tests were performed in the laboratory of the late Dr. F. O. Boerner at the University of Pennsylvania Hospital.



period of hospitalization, averaging about 5,000 calories per day, and were of high protein and high carbohydrate composition. They were allowed about 50 grams of dairy fats per day while at the Hepatitis Center.

On return, these patients were hospitalized for a period of several days, during which an interim history was taken, a careful physical examination made, and a battery of liver function tests performed.

In the interim history, particular attention was paid to intercurrent disease, gastrointestinal complaints (especially right upper quadrant pain), epigastric pain, abdominal discomfort and flatulence, nausea, anorexia and weight loss. A precise inquiry was made into their physical activity and as to the actual amount of alcohol taken. The latter inquiry needed particular care by the physician, as all of the patients on discharge from the hospital had been told not to drink for a period of at least three months. Even though reassured, it is probable that many soldiers were reluctant to admit their actual alcohol consumption.

For purposes of comparison patients were classified on the basis of the amount of alcohol consumed in the interim as heavy, moderate and light drinkers, and unless specifically mentioned, drinking alcohol began shortly after discharge. As "heavy" drinkers we have classified those who consumed daily enough to fit into the group classified by Ratnoff and Patek<sup>6</sup> as "alcoholism," i.e., the *daily regular* consumption of one quart of wine, six glasses of beer, or six ounces of whiskey or distilled spirits. "Moderate" drinkers were those who drank an average of not much more than two ounces of distilled spirits every day, and those who drank less than two ounces of whiskey or two liters of beer, whether intermittently or regularly were classed as "light" drinkers.

Physical activity during the interim period was classified as "heavy" if the duty which the patient had actually been performing since discharged involved strenuous manual labor, heavy lifting, or truck driving. "Moderate" activity referred to such military duty as garrison guard duty where considerable walking but little heavy labor was required. "Light" physical activity included sedentary duties and the duties of flight personnel not requiring handling of cargo. In addition to his occupation, a man's athletic activities were taken into consideration. Thus a clerk who played basketball every night was classified as having had "heavy" rather than "light" activity.

On physical examination particular attention was paid to estimation of the size of the liver both by percussion and palpation, and to the presence of tenderness on palpation.<sup>14, 15</sup> The weight was taken for comparison with that recorded at the end of the previous hospitalization.

The following liver function tests were performed on all patients, and are listed along with what is considered at the Hepatitis Center as the upper limit of normal:

Test	Upper Limit of Normal
Cephalin-cholesterol flocculation <sup>16</sup>	<1 + at 24 hours <2 + at 48 hours
Thymol turbidity <sup>17</sup>	4 units
Total serum bilirubin <sup>18</sup>	<1.5 mg. per cent
One minute prompt direct bilirubin <sup>18</sup> as modified <sup>19</sup>	0.2 mg. per cent
Bromsulfalein excretion photoelectrically determined after 5 mg./kilo body weight <sup>20</sup>	Retention of 5 per cent after 45 minutes
Urine bilirubin	1 +
Qualitative Harrison spot test as modified <sup>21</sup>	
Urine urobilinogen (morning specimen) <sup>22</sup>	1.5 Ehrlich units/2 hours

## RESULTS

Of the 114 patients who returned, 68 had been discharged six months to one year previously without clinical or laboratory evidence of residuals of hepatitis. The vast majority had been on graded exercises before discharge culminating in a five-mile hike. The remaining patients had had what is usually considered laboratory or clinical evidence of residual hepatitis, most frequently laboratory findings of a minor nature. These two groups have been classified as "convalescent" and "presumably cured," and are dealt with separately in tables 1 and 2.

In table 1 are shown the findings on readmission of the patients discharged as "presumably cured," and in table 2 the findings on readmission of those discharged with residuals ("convalescent"). Table 3 contains the findings on the "convalescent" group both at original discharge and on readmission. Table 4 contains the readmission findings on the total group studied.

Of the 114 cases, 28 patients were classified as "heavy," 23 as "moderate" and 35 as "light" drinkers, while 26 denied the consumption of any alcohol in the interim period. Two patients could not be classified on their alcoholic intake because of inadequate information on the charts. Thirty-five patients had been engaged in "heavy" physical activity during the interim, 40 in "moderate" and 39 in "light."

Surprisingly enough, a higher percentage of the patients in the "presumably cured" group (41 per cent) returned with residuals than did the "convalescent" group (28.3 per cent) though of course the small numbers do not lend this any significance. Of the total group, 35.9 per cent had residuals on return, but as will be mentioned later, the "residuals" in the vast majority consisted of slight elevations in the thymol turbidity.

Surprisingly few (14 patients or 12 per cent) had any symptoms, and of those who did, six complained of mild indigestion, three complained of

TABLE I

Findings on 68 Patients Discharged as Presumably Cured  
Six Months to One Year Previously

	No.	%	Alcohol				Activity		
			Heavy	Mod.	Light	Total Abs.	Heavy	Mod.	Light
Patients discharged as presumably cured six months to one year previously	68	100	19	14	24	11	23	22	23
Patients without residuals on reëxamination	40	59	10	8	17	5	15	13	12
Patients with residuals on reëxamination	28	41	9	6	7	6	8	9	11
Residuals on 28 Patients	12								
Symptoms			5	2	2	3	5	2	5
Without other findings	5		1	1	2	1		2	3
With hepatomegaly	2		1	1			1		1
With impaired function	4		2			2	3		1
With hepatomegaly and impaired function	1		1				1		
Hepatomegaly	5		3	2			2	1	2
Without symptoms or other findings	2		1	1				1	1
With symptoms	2		1	1			1		1
With symptoms and impaired function	1		1				1		
Impaired liver function	21		10	3	5	3	9	5	7
With abnormal thymol turbidity	14		6	3	3	2	5	5	4
With abnormal cephalin cholesterol flocculation	2		2				2		
With bromsulfalein dye retention	5		2		2	1	2		3

Note: Number of patients with more than 1 residual = 10.

occasional right upper quadrant pain, four of occasional intolerance to fatty food, and one of bouts of epigastric pain. Only one of the patients with symptoms had any significant physical findings on review, and only four had laboratory evidence of liver dysfunction, namely slight elevations of the thymol turbidity test, the highest being 5.69 units. All other laboratory functional tests were within normal limits.

On physical examination, one patient was found to have a number of typical "spider" telangiectases scattered over his chest. The only other finding in this particular case was that the liver was tender and was palpable one finger's-breadth below the costal margin.

From the tables it may be seen that neither the amount of alcohol ingested nor the interim activity could be correlated with the residuals found in this group. This is true of both the convalescent and the presumably cured groups. For example, 42.8 per cent of the heavy drinkers had residuals on

TABLE II  
Findings on 46 Patients Discharged with Residuals Six  
Months to One Year Previously

	No.	%	Alcohol				Activity		
			Heavy	Mod.	Light	Total Abs.	Heavy	Mod.	Light
No. of patients in group	46								
No. of patients without residuals on return	33	71.7	4	5	14	10	9	11	13
Patients with residuals on reëxamination	13	28.3 100%	3	5	0	5	4	7	2
Residuals									
Symptoms	3		1	1		1		2	1
Without other findings	2			1		1		2	
With hepatomegaly	0								
With impaired function	1		1						1
With hepatomegaly and impaired function	0								
Hepatomegaly		None							
Impaired liver function	11		3	3		5	4	5	2
With abnormal thymol turbidity	10		3	3		4	3	5	2
With abnormal cephalin cholesterol flocculation	1					1	1		
With bromsulfalein dye retention	0								

Number of patients with more than 1 residual = 1.

TABLE III  
Comparison of Tests on 46 Patients Discharged with Residuals of  
Hepatitis Six Months to One Year Previously

	On Discharge						On Readmission					
	All Positive Test	Hepatomegaly	Cephalin-Chol. Flocculation	Thymol Turbidity	Bromsulfalein	Patients with More Than One Positive Finding	All Positive Test	Hepatomegaly	Cephalin-Chol. Flocculation	Thymol Turbidity	Bromsulfalein	Patients with More Than One Positive Finding
Heavy drinkers	10	1	1	4	4	0	3	0	0	3	0	0
Moderate drinkers	9	2	1	1	5	0	2	0	0	2	0	0
Light drinkers	12	1	3	2	6	1	2	0	0	2	0	0
Total abstainers	16	2	0	6	8	0	6	0	0	6	0	0
Total number	47	6	5	13	23	1	13	0	0	13	0	0
Heavy workers	14	2	2	4	6	0	4	0	0	4	0	0
Moderate workers	16	2	0	6	8	1	6	0	0	6	0	0
Light workers	17	2	3	3	9	0	3	0	0	3	0	0
Total number	47	6	5	13	23	1	13	0	0	13	0	0

Number of patients with more than 1 residual abnormality = 1.

TABLE IV

Comparison of Residuals in "Presumably Cured" Group (68 Patients) and "Convalescent" Group (46 Patients) with Reference to Alcohol and Activity

	"Presumably Cured"		"Convalescent"		Totals	
	No. of Patients	% of Group	No. of Patients	% of Group	No. of Patients	%
Alcohol						
Heavy	9	13.2	3	6.6	12	10.5
Moderate	6	8.8	5	10.8	11	9.6
Light	7	10.2	0		7	6.2
Total abstainers	6	8.8	5	10.8	11	9.6
	28	41.0	13	28.2	41	35.9
Activity						
Heavy	8	11.7	4	8.7	12	10.5
Moderate	9	13.2	7	15.2	16	14.1
Light	11	16.1	2	4.3	13	11.3
	28	41.0	13	28.2	41	35.9

Total number of residuals in "Presumably Cured" Group = 28 (41.0%).

Total number of residuals in "Convalescent" Group = 13 (28.2%).

return, but those who did not drink anything had residuals in 42.3 per cent of their number.

	No. Patients in Group	No. with Residuals	%
Alcohol			
Heavy	28	12	42.8
Moderate	23	11	47.9
Light	35	7	20.0
Total abstainers	26	11	42.3
Activity			
Heavy	35	12	34.3
Moderate	40	16	40.0
Light	39	13	33.4

The light drinkers had fewer residuals than any of the other groups, including the total abstainers, but this is probably not significant.

Of the six patients who had had a palpable liver at the time of discharge none had palpable livers on return. The activities of these six and their alcohol consumption were as follows:

Patient	Time Interval Since Discharge	Interval Activity	Alcohol
21340	11 months	Moderate	Heavy
21615	7 months	Moderate	Heavy
21653	10 months	Light	Light
21718	9 months	Heavy	Moderate
21899	8 months	Light	Moderate
23041	8 months	Moderate	Abstainer

Five subjects were found to have a palpable liver (none more than one finger's-breadth on the check-up examination). None of these had had a palpable liver at the time of discharge. The record of their interval activities and alcohol consumption is as follows:

Patient	Time Interval Since Discharge	Interval Activity	Alcohol
21426	10 months	Heavy	Heavy
21620	6 months	Moderate	Heavy
21673	9 months	Moderate	Moderate
22460	8 months	Heavy	Moderate
21645	11 months	Light	Moderate

Of the laboratory tests of liver function, it might be said that in both the presumably recovered group and in the "convalescent" group (those discharged with *any* abnormal finding) most of those which were positive, or abnormal, were not significantly so.

Laboratory studies of liver function demonstrated slight increase in thymol turbidity in 23 cases. All the other tests performed were within normal limits. Four of the 23 had had an abnormal thymol test on discharge from the hospital. There were nine others with abnormal thymol turbidity on discharge who returned with normal values.

The number of patients in the total group with positive thymol turbidity tests on readmission for check-up was 24.

No.	Interim Alcohol	Units of Thymol Turbidity	
		Range	Average
9	Heavy	6.3-4.3	5.3
6	Moderate	6.0-4.3	5.1
3	Light	9.6-4.3	5.6
6	Total abstainers	7.5-4.06	4.9
24			
Activity			
8	Heavy	7.12-4.06	5.5
10	Moderate	9.6-4.3	6.4
6	Light	7.5-4.3	5.1
24			

Of 13 patients who were discharged from the hospital with a slight elevation of the thymol turbidity test, nine returned with normal tests, and four with the test unchanged but without other abnormalities.

It is interesting to note the relatively large amounts of alcohol consumed. As any classification does not quite convey the picture, in table 5 are shown

TABLE V

Findings on Heavy Drinkers at Time of Discharge and on Follow-Up

Case No.	Time Elapsed Since Discharge	Abnormality on* Initial Discharge	Alcohol Consumption per Day		Interval Occupation	Abnormality on* 2nd Admission
			Spirits in Ounces	Beer in c.c.		
23564	6 months	TT 7.19 CCF 3/3	6- 7 whiskey	1000	Sedentary	TT 5.5
23203	7 months	TT 5.25	7- 8 cognac	3000	Moderate	TT 5.69
21619	7 months	None	7- 8 whiskey	2000	Light	TT 4.37
21615	7 months	Liver palpable 1 FB	8- 9 whiskey	1500-2000	Light	None
21620	6 months	None	6-12 whiskey	5000	Light	TT 4.37 CCF 2/2
21825	6 months	None	10-12 whiskey	1500-2000	Heavy	None
21827	8 months	None	3- 4 whiskey	3000-4000	Sedentary	None
21923	12 months	None	7 whiskey	None	Sedentary	None
21940	12 months	BSP 7%	15-20 whiskey	1500-2000 b.i.w.*	Heavy	None
21972	8 months	None	4 whiskey	3000-4000	Heavy	TT 4.4
21976	7 months	None	3- 4 whiskey	3000-4000	Light	None
22064	11 months	None	4- 5 whiskey	1500	Heavy	None
22093	11 months	None	8 whiskey	1500-2000	Heavy	None
22432	9 months	None	8- 9 whiskey	1500-2000	Heavy	None
22458	10 months	None	6 whiskey	2000	Light	BSP 5.25%
22552	12 months	None	2- 3 whiskey	5000-7000	Sedentary	None
20751	12 months	None	6- 7 whiskey	10,000	Moderate	None
20781	6 months	None	4- 5 whiskey	2000	Moderate	None
20800	8 months	None	4- 5 whiskey	4000	Heavy	None
20801	9 months	None	5- 6 whiskey	5000-6000	Heavy	TT 6.3 CCF 2/2
20886	12 months	None	8- 9 cognac	None	Heavy	TT 5.19
21340	11 months	BSP 10%	3 whiskey	3500-4000	Moderate	None
21393	6 months	BSP 10%	4- 5 whiskey	None	Moderate	TT 7.12
21427	9 months	BSP 10%	6 whiskey	1000	Light	None
21426	10 months	TT 4.6	5- 6 whiskey	2000	Heavy	TT 4.6 palp. liver
21431	7 months	None	6 whiskey	2000	Light	BSP 5.25
25583	6 months	None	5 whiskey	3000	Heavy	Mild fat intolerance

\* TT—Thymol turbidity.

CCF—Cephalin cholesterol flocculation.

BSP—Bromsulfalein.

b.i.w.—Twice weekly.

the findings in those patients classified as "heavy" drinkers, both on the original and re-check admissions, together with their actual consumption of alcohol.

## DISCUSSION

From these findings it appears that the patients in this series who consumed relatively large amounts of alcohol in the period of convalescence six to 12 months after acute hepatitis showed no more evidence of post-hepatic liver damage than did those patients who consumed smaller amounts of alcohol. This appears to be true both of those discharged as "presumably cured" and those discharged with minor residuals. Though more difficult

to assay, it also appears that there was little difference between the group which had been very active physically and those who were not. These findings are somewhat at variance with those reported by Barker, Capps and Allen<sup>12</sup> who found that alcohol in excess could definitely provoke a relapse. Sporadic infectious hepatitis, as it was seen in Germany during the period of this study, presented several differences from the *epidemic* infectious hepatitis so well studied by Barker and his colleagues. It is important to emphasize that the findings of Barker and others referred to special conditions. It should be remembered that the troops now acquiring infectious hepatitis in Germany are well nourished and in good physical condition at the time they acquire the disease. They have also been leading a relatively non-strenuous garrison life while those studied in the Mediterranean and in the Southwest Pacific had been subjected to the fatigue and exposure of actual warfare in addition to having been on inadequate and unappetizing field rations for a long time.

It is possible that the severity of the disease is related to the nutritional state at the time of infection as well as to possible differences in the strains of the virus. The data presented suggest that the sporadic infectious hepatitis seen in well-nourished individuals is a more benign disease as regards chronicity, residuals, and relapses than the epidemic variety occurring under the circumstances of war, and that overindulgence in alcohol or in physical activity during the recovery period in this form of the disease has little effect on its outcome.

### SUMMARY

One hundred and fourteen American soldiers were studied six months to one year after hospitalization for an attack of infectious hepatitis acquired in Germany. Of these, 46 had been discharged from the hospital with slight residual abnormalities, and 68 as presumably cured. Only slight differences were noted between the two groups on reexamination after the interval, and there were relatively more residuals present in the group discharged as presumably cured than in those discharged with slight residuals. When reexamined with particular reference to their interim activity and alcohol, it appeared that neither of these factors played a significant rôle in the appearance of residuals in either group.

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# THE NOCTURNAL GASTRIC SECRETION IN PATIENTS WITH BENIGN GASTRIC ULCER\*

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## INTRODUCTION

THE results of studies on the nocturnal gastric secretion of normal individuals and of patients with duodenal ulcer, gastric ulcer and gastric carcinoma have been summarized in a previous publication.<sup>1</sup> Although the number of patients with gastric ulcer in the original series was small, the data were sufficiently constant to indicate certain trends. The series now has been increased sufficiently to permit definite conclusions. The purpose of this paper is to describe in detail the periodicity and variability of the nocturnal gastric secretion in such patients and to compare them with normal subjects and patients with duodenal ulcer. To our knowledge, a similar study has not been presented heretofore.

## METHODS

The methods employed and the criteria used in the selection of subjects have been described previously.<sup>1, 2</sup> The conditions of study were identical in all. Fifty-seven observations were obtained in 25 patients with benign gastric ulcer. Microscopic evidence of the benignity of the lesion was obtained in fourteen. The presence of a benign ulcer was definitely proved by roentgen-ray examination, gastroscopy, the clinical course, or by a combination of all three in 11 individuals. All patients were admitted to the hospital because of ulcer distress and a crater was demonstrated roentgenologically in each case.

## RESULTS

### *Total Night Secretion*

*Volume.* The individual volumes of the total night secretion ranged from 133 c.c. to 1,444 c.c., averaging 600 c.c. (table 1): The volume was less than 1,000 c.c. in 86 per cent of the studies. It ranged between 300 and 800 c.c. in two-thirds (figure 1). Variations were observed not only among individuals but also in the same person on different nights. The individual variation for the group averaged 25 per cent.

*Free Acidity.* The free acidity (concentration of free HCl) of the total night secretion ranged from 0 to 59 clinical units, averaging 21 (table 1). It was less than 40 clinical units in 87 per cent of the studies and less than

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

20 clinical units in more than 50 per cent (figure 1). Anacidity in the total night secretion was observed in 13 per cent. (Free acid was present in all cases in response to histamine stimulation.)

The free acidity varied in the same individual on different nights. It is of interest that the variation in the free acidity of the total excretion exceeded five clinical units in only 12 individuals.

*Mg. Free HCl.* The output of free HCl for the 12 hour period averaged 454 mg., the range being 0 to 2,713 mg. (table 1). It was less than 1,000

TABLE I  
The 12-Hour Continuous Nocturnal Gastric Secretion in  
Patients with Benign Gastric Ulcer  
(8:30 p.m. to 8:30 a.m.)

Case		Volume (c.c.)	Free Acid (Cl. Units)	Total Output of HCl (Mg.)
(Age)	(Sex)			
A. P. 47	M	202	0	0
		594	3	56
H. A. 47	M	861	12	366
		566	6	116
A. Z. 49	M	736	3	83
		719	5	120
M. C. 34	F	553	35	701
		524	37	714
I. B. 57	M	1122	3	116
		1014	11	423
V. L. 58	M	385	14	200
		335	2	24
		374	0	0
J. W. 60	M	432	1	17
		531	5	105
J. M. 60	M	1018	37	1327
E. F. 63	M	547	9	176
		1009	25	930
		558	5	99
		642	2	40
		449	2	33
		540	4	79
L. H. 61	M	628	20	446
		638	20	461
R. M. 45	M	502	2	38
		371	2	30
A. N. 66	F	415	24	326
		396	23	332
C. G. 60	M	1444	21	1127
		1113	25	1022

TABLE I—*Continued*

Case		Volume (c.c.)	Free Acid (Cl. Units)	Total Output of HCl (Mg.)
(Age)	(Sex)			
T. S. 78	M	133 258 295	0 0 2	0 0 18
E. S. 58	M	686 1275	21 59	536 2713
C. M. 32	F	308 706	29 29	328 746
M. M. 71	F	167 172 158	0 0 0	0 0 0
C. O. 43	M	585 440	53 50	1120 801
G. P. 43	F	500 460	21 43	388 715
W. G. 58	M	645 378	7 20	155 273
J. E. 63	M	694 1024	23 10	568 386
E. H. 58	M	549 359	14 0	277 0
J. J. 30	M	601 480	30 42	657 738
J. D. 50	M	619 844 1122	20 22 57	440 662 2331
C. H. 62	M	692 859	50 39	1257 1215

mg. in 85 per cent of the studies and below 500 mg. in approximately two-thirds; anacidity was present in 22 per cent of the latter studies; less than 200 mg. were obtained in 57 per cent. The acid output exceeded 2,000 mg. in only 2 per cent (figure 1). The individual variation for the entire group averaged 26 per cent.

Individuals secreting a small amount of acid on one night in the vast majority of instances produced a small amount on successive nights; a similar constancy existed for patients with a high secretory rate. This correlation was observed also for both the volume and free acid concentration.

#### THE HOURLY VARIATION IN NOCTURNAL GASTRIC SECRETION

*Volume.* The gastric secretion was continuous; rarely, there was a lack of gastric juice for one hour; in no instance was there an absence of secretion

for as long as two hours. The highest hourly volume was 196 c.c.; the average 50 c.c.

The *average* hourly secretion decreased gradually until 5:30 a.m.; there tended to be a gradual increase during the last quarter of the night (5:30

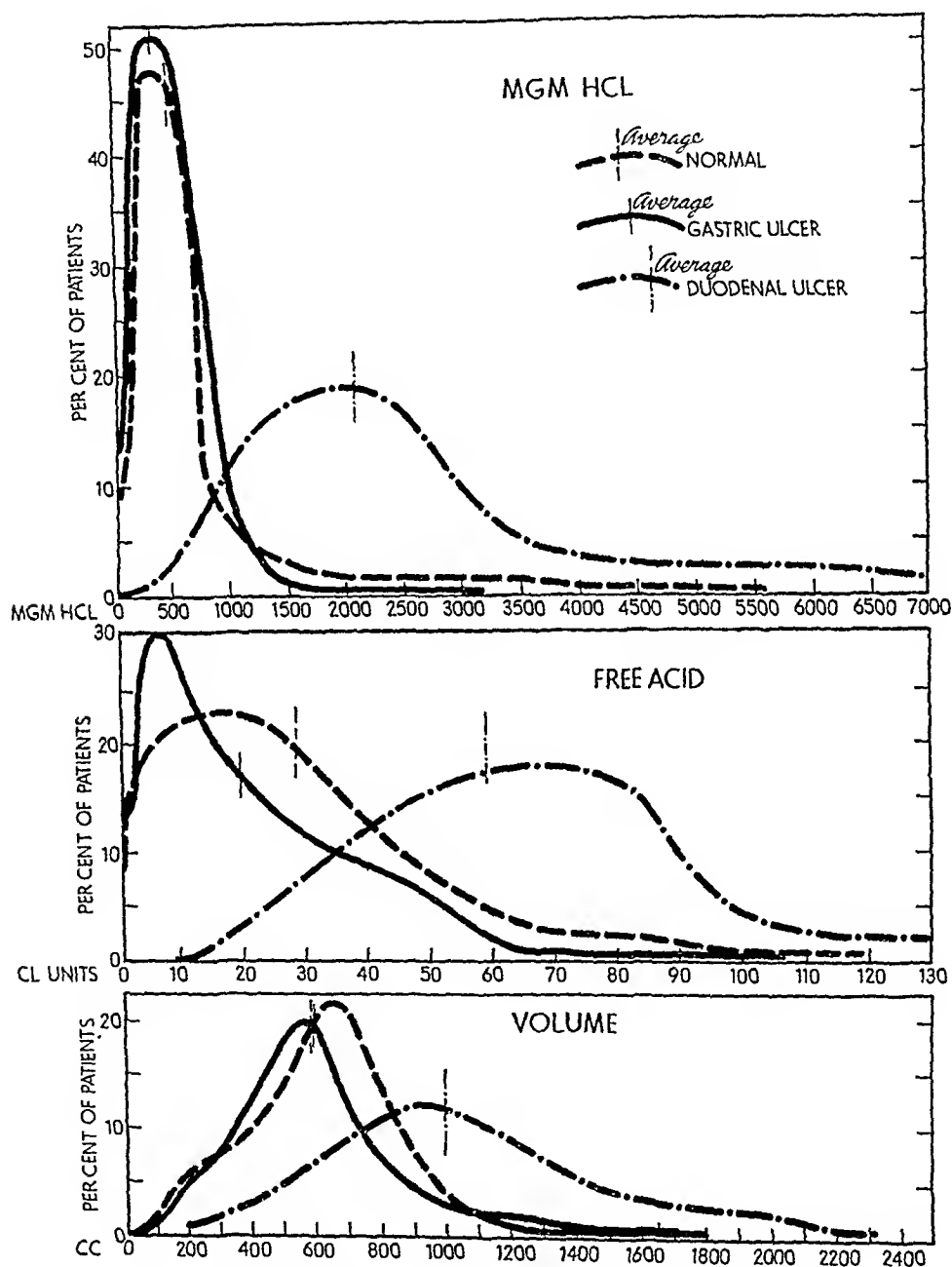


FIG. 1. Distribution curves—nocturnal gastric secretion.

a.m.—8:30 a.m.) (figure 2). The lowest output occurred between 3:30 a.m. and 5:30 a.m. The average volume was slightly greater during the first half of the night than during the last half (table 2).

There was a marked variation in the periodicity of the night secretion not only between subjects, but also in the same individual (figure 3). The rate of secretion was not constant; the fluctuations from one hour to the next were as great as 500 to 600 per cent. The hourly variation for the entire group averaged approximately 50 per cent. Four representative patterns are shown in figure 4. In this series, the maximum hourly volume occurred prior to 2:30 a.m. in all but seven of the studies.

TABLE II

The Average Volume, Free Acidity and Milligrams of Free Hydrochloric Acid Secreted During Quarterly Periods of the Night (Patients with Gastric Ulcer)

	Volume (c.c.)	Free Acidity (Cl. Units)	Hydrochloric Acid (Mg.)
8:30 p.m.-11:30 p.m.	184	29	193
11:30 p.m.- 2:30 a.m.	142	20	102
2:30 a.m.- 5:30 a.m.	114	20	82
5:30 a.m.- 8:30 a.m.	160	14	80

*Free Acidity (Concentration of Acid).* The secretion of acid, in contrast to the volume, was not continuous in all cases. Acid was secreted continuously throughout the night in only 19 per cent of the studies. Anacidity for two consecutive hours or more was noted in 76 per cent; in 13 per cent anacidity was present throughout the entire night. In only one subject\* (M. M., table 1) did the anacidity persist on successive nights. The temporary anacidity (several hours) usually occurred after midnight.

TABLE III

The Average 12-Hour Nocturnal Gastric Secretion in Normal Individuals and in Patients with Gastric and Duodenal Ulcer

	Volume (c.c.)	Free Acid (Cl. Units)	Total Output of HCl (Mg.)
Normal	581	29	661
Gastric ulcer	600	21	454
Duodenal ulcer	1004	61	2242

The highest free acidity in one hour was 80 clinical units; the hourly value for the entire group averaged 21 clinical units. The free acidity was persistently below 50 clinical units throughout the night in 71 per cent of the studies. In no instance was it persistently greater than 50 clinical units throughout the night.

\* After histamine stimulation the free acidity reached a peak of eight clinical units.

The hourly free acidity frequently equaled or exceeded that produced in response to histamine, usually among individuals with a maximum histamine response below 40 clinical units.

There was a gradual decrease in the *average* hourly concentration of acid as the night progressed (figure 2). The average free acidity was

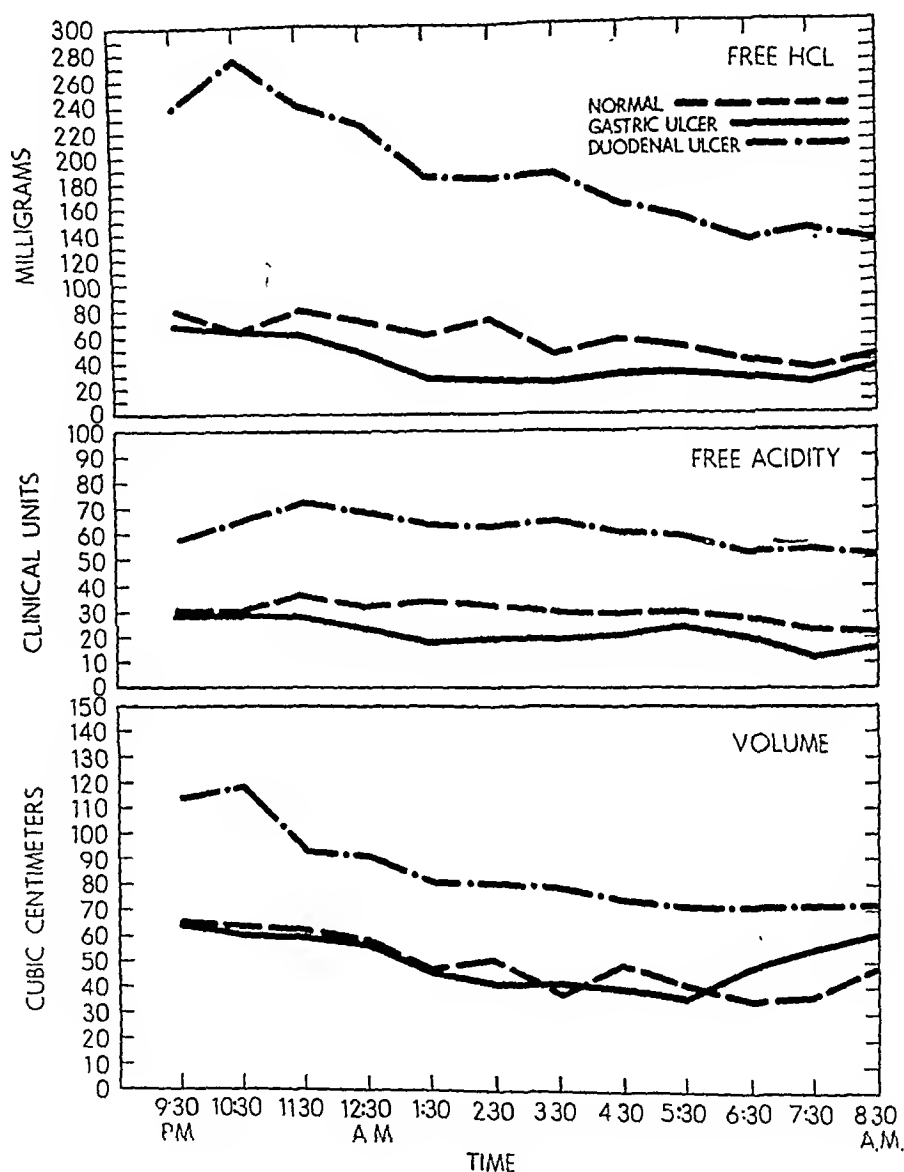


FIG. 2. Nocturnal gastric secretion—average hourly output.

greater during the first half than during the second half; the greatest decrease occurred during the last three hours (table 2).

Representative patterns are shown in figure 5. As with the volume, there was a marked variation from one individual to another. In general, the maximum concentration of acid may occur at any hour of the night. In

81 per cent of the studies it occurred before 2:30 a.m. In practically all there was a gradual decrease during the night in the same individual; however, increasing concentrations were noted in a few instances.

Varying patterns were noted in the same individual on different nights even though the conditions of study were identical (figure 3).

*Milligrams of Free Hydrochloric Acid.* The *average* hourly output of free hydrochloric acid gradually decreased during the night (figure 2). The amount secreted during the first half of the night was significantly greater than that during the second half (table 2), the largest decrease occurring between the hours of 11:30 p.m. and 2:30 a.m.

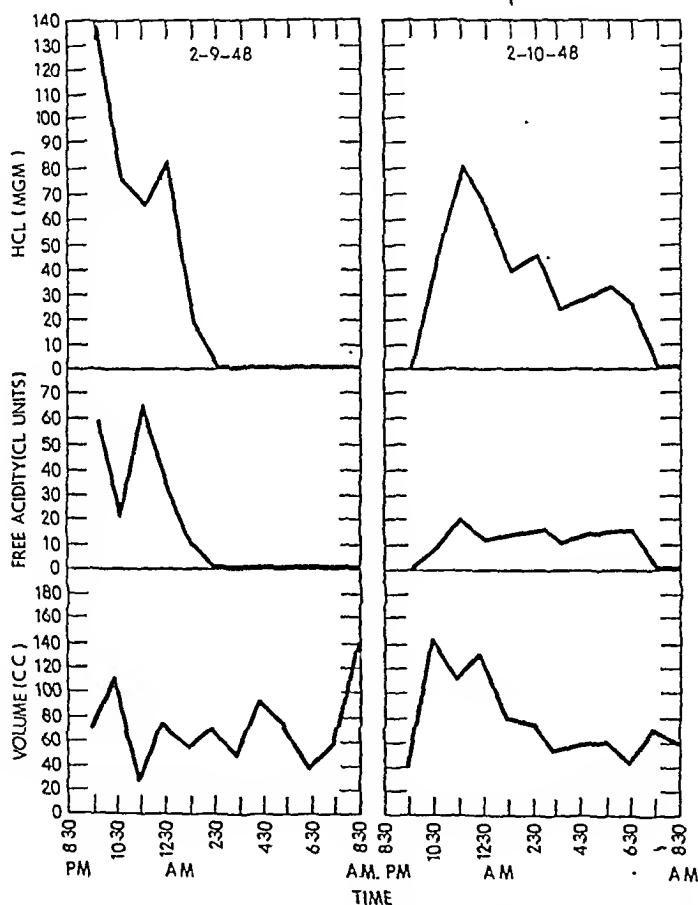


FIG. 3. Hourly variation of the volume free acidity and output of hydrochloric acid in the same individual (gastric ulcer).

The rate of secretion of acid was not constant. Rarely were similar quantities of acid secreted for two consecutive hours. Figure 4 shows the representative patterns obtained. Although the maximum hourly secretion of hydrochloric acid may occur at any time during the night, in 87 per cent it occurred prior to 2:30 a.m. A progressively increasing hourly output of acid was not observed in this series. In the few studies in which the maxi-



imum hourly secretion occurred after 2:30 a.m., the higher values were obtained during the waking hours (6:30 a.m. to 8:30 a.m.). However, in 55 per cent of the studies no free acid was obtained after 6:30 a.m. The amount of acid persistently exceeded 50 mg. throughout the night in only 2 per cent of the patients.

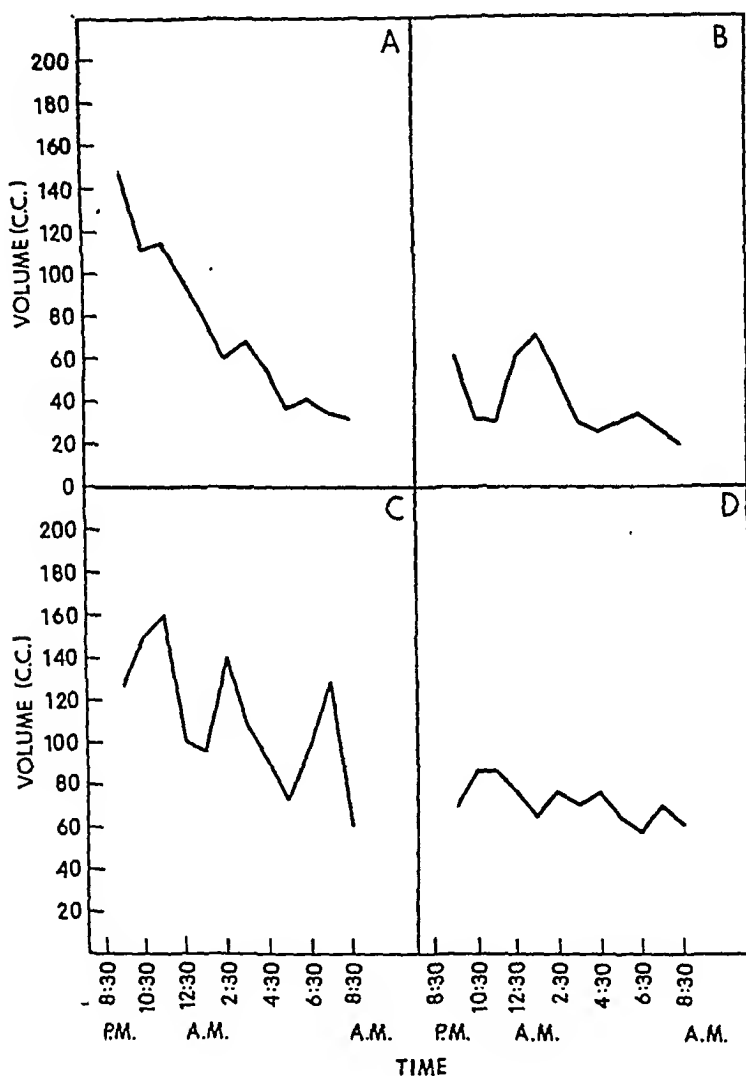


FIG. 4. Representative patterns in the hourly volume of gastric secretion during the night in patients with gastric ulcer.

The largest individual quantity of acid secreted in one hour was 470 mg.; the hourly output for the entire group averaged 38 mg.

Varying patterns were also present in the same individual on different nights (figure 3). It is of interest that the majority of individuals with long periods of anacidity during one night manifested similar periods of anacidity on successive nights.

*Comparison with Normal Individuals and Patients with Duodenal Ulcer\**

*Volume.* This study indicates that there is no significant difference in this respect between patients with benign gastric ulcer and normal individuals (table 3); the values averaging 600 c.c. and 581 c.c., respectively. The distribution curves of each practically overlap throughout (figure 1). On the other hand, the total volume in patients with duodenal ulcer, averaging 1,000 c.c. is significantly greater (table 3). In patients with duodenal ulcer the volume was less than 800 c.c. in only 32 per cent of the studies and exceeded 1,000 c.c. in 47 per cent. In patients with gastric ulcer it exceeded 1,000 c.c. in only 14 per cent (figure 1).

Gastric secretion was continuous in all three groups. In only two instances was there an absence of secretion for as long as two hours and lack of secretion for as long as one hour was exceedingly rare.

Similarly, in all subjects studied, the rate of secretion varied from hour to hour in the same individual. In duodenal ulcer patients, it was not uncommon for an individual to maintain a constantly high secretory rate for several consecutive hours (i.e. more than 75 c.c. per hour). Persistent hypersecretion was rare in normal individuals and in patients with gastric ulcer. Although there was a tendency for the average hourly secretion to decrease gradually during the night in all three groups, the secretory rate in the duodenal ulcer series consistently remained at a distinctly higher level throughout the night (figure 2).

In all three groups, in the vast majority of the subjects, the maximum hourly volume occurred prior to 2:30 a.m.

*Free Acidity.* The free acidity of the total night secretion varied in the three groups studied, the average being 21 clinical units in gastric ulcer, 29 in the normals and 61 clinical units in duodenal ulcer (table 3). In the gastric ulcer series it was less than 40 clinical units in 87 per cent of studies and less than 20 in 55 per cent; in no instance did it exceed 60 clinical units. In the normal group, the free acidity was less than 40 clinical units in 72 per cent of the studies and less than 20 in only 38 per cent; it exceeded 60 clinical units in 10 per cent. On the other hand, in patients with duodenal ulcer it exceeded 60 clinical units in 50 per cent of the studies; values below 40 clinical units were obtained in only 20 per cent (figure 1).

The individual fluctuations in free acid were greater in both the normal subjects and duodenal ulcer patients than in the gastric ulcer group. Variations larger than five clinical units were observed in only 12 individuals of the latter group. However, in the majority of patients with gastric or duodenal ulcer, a high concentration of acid on one night was repeated on successive nights. A similar constancy was observed in patients with low concentrations. This correlation did not necessarily hold true in normal individuals.<sup>2</sup>

\* For complete data of normal individuals and patients with duodenal ulcer see references 1, 2 and 3.

Whereas, in patients with duodenal ulcer the secretion was continuous in all studies except three, it was not continuous in the vast majority of normal individuals and patients with gastric ulcer. Periods of anacidity for one or more hours were noted in 70 per cent of the normal studies, and in 81 per cent of the gastric ulcer group.

The concentration of acid was persistently below 50 clinical units throughout the night in 71 per cent of the gastric ulcer studies, in only

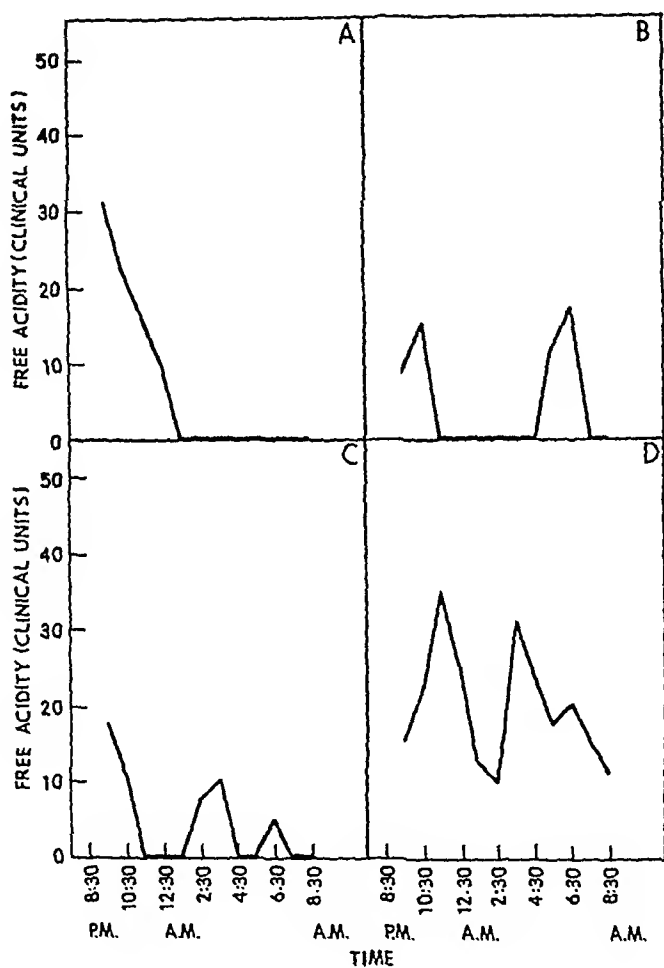


FIG. 5. Representative patterns in the hourly free acidity of the nocturnal gastric secretion in patients with gastric ulcer.

44 of the normal group and 35 per cent of the duodenal ulcer studies. On the other hand, in none of the gastric ulcer patients was it persistently greater than 50 clinical units; values higher than 50 were noted in 6 per cent of the normal group and in 35 per cent of the duodenal ulcer series.

A gradual decrease in the average hourly concentration occurred in both the duodenal and gastric ulcer groups, whereas in normal individuals it remained remarkably constant throughout the night (figure 2). However, as emphasized in a previous publication<sup>2</sup> composite curves are not repre-

sentative, since a high concentration in one subject is offset by a low concentration in another. Nevertheless, the average hourly concentration is highest in patients with duodenal ulcer and lowest in gastric ulcer patients.

In all three groups the maximum hourly concentration in the vast majority of instances occurred prior to 2:30 a.m. In general, the concentration gradually decreased during the night in the same individual. The

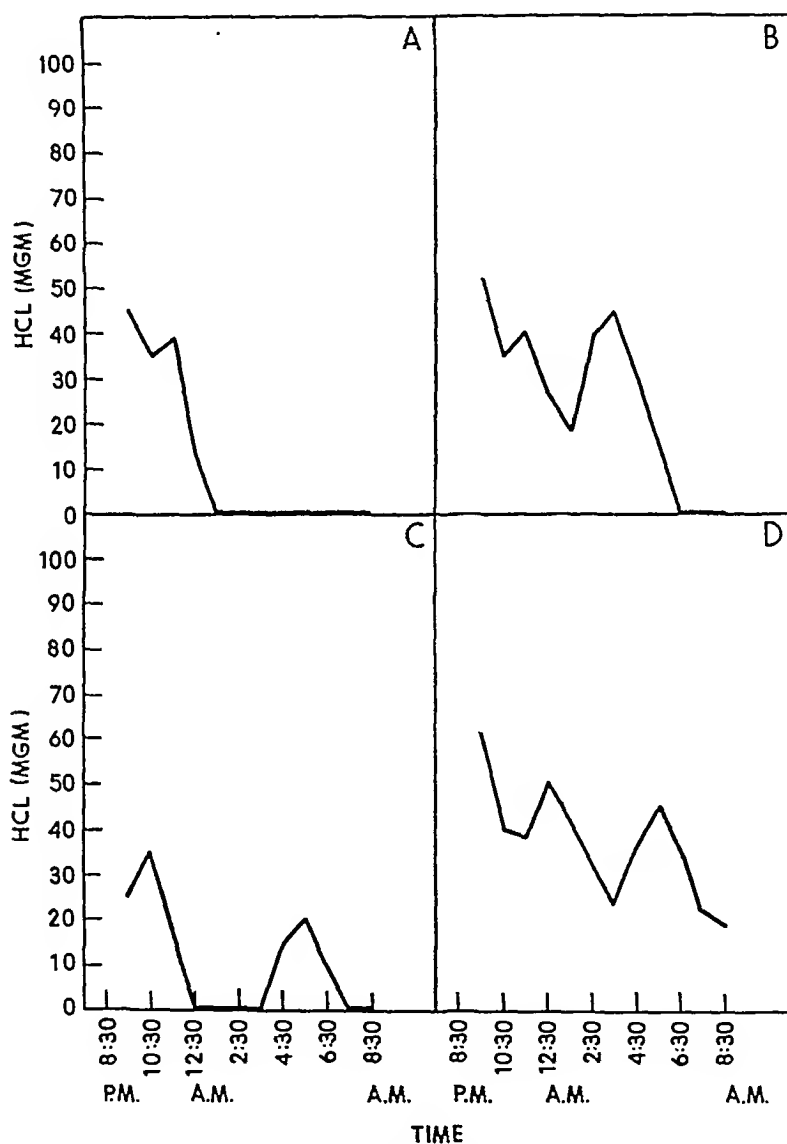


FIG. 6. Representative patterns in the hourly output of hydrochloric acid during the night in patients with gastric ulcer.

pattern varied not only from one individual to another but also in the same individual on different nights.

*Mg. Free Hydrochloric Acid.* The amount of free HCl for the 12 hour period was lowest in patients with gastric ulcer, the average being 454 mg.; the average for the normal group was 661 mg. and for patients with duodenal

ulcer 2,242 mg. (table 3). Although there was some overlap in the distribution, the differences are statistically significant (figure 1). In the gastric ulcer group, it was less than 1,000 mg. in 85 per cent of the studies and below 500 mg. in approximately two-thirds. Of the latter, anacidity was present in 22 per cent and less than 200 mg. were obtained in 57 per cent. In the normal individuals, the output was less than 1,000 mg. in 84 per cent of the studies and below 500 mg. in 50 per cent. Of the latter, approximately two-thirds were below 200 mg., no individual having a complete anacidity. In contrast, the output in duodenal ulcer patients exceeded 1,000 mg. in 81 per cent of the studies and 2,000 mg. in more than 50 per cent. An output less than 500 mg. was noted in only one instance.

There is a gradual decrease in the average hourly secretion of free hydrochloric acid in all three groups studied (figure 2). The hourly secretion averaged 38 mg. in gastric ulcer patients as compared with 55 mg. in normal individuals and 187 mg. in patients with duodenal ulcer. In two-thirds of the duodenal ulcer patients the output of HCl for the same hour exceeded the average output of the normal and gastric ulcer patients.

In patients with duodenal ulcer the amount was persistently greater than 50 mg. throughout the night in 63 per cent of the studies and more than 100 mg. in 32 per cent. In the normal group it was persistently greater than 50 mg. in 12 per cent and persistently greater than 100 mg. in only 4 per cent. In contrast, in only 2 per cent of the gastric ulcer patients was the hourly amount persistently greater than 50 mg. Free acid was not obtained after 6:30 a.m. in 55 per cent of the patients with gastric ulcer, in only 18 per cent of the normal group; anacidity was never observed in patients with duodenal ulcer.

The rate of secretion in the same individual was not constant in all three groups. In the majority of individuals the maximum hourly secretion of hydrochloric acid occurred prior to 2:30 a.m. Varying patterns were present from individual to individual and also in the same individual on different nights. As a rule, however, an individual with a high secretion on one night, manifested a relatively high secretion of acid in successive nights. This also held true for individuals with a relatively low secretion rate.

#### COMMENT

This study demonstrates statistically significant gastric secretory differences between patients with gastric ulcer, normal individuals and patients with duodenal ulcer. The volume of the night secretion in gastric ulcer patients is significantly lower than that of duodenal ulcer patients. On the other hand, there is no significant difference between gastric ulcer patients and normal individuals. The concentration of free hydrochloric acid and the amount of acid secreted is lowest in patients with gastric ulcer when compared with normal individuals and patients with duodenal ulcer.

No correlation existed between the amount of secretion and the location

of the ulcer in the stomach, duration of symptoms or the age of the patient. There appears to be no consistent correlation between the degree of gastritis as determined gastroscopically, with the amount of acid produced. However, the secretion is relatively lower in individuals with an associated atrophic gastritis as compared with those in whom atrophy is not demonstrated.

The explanation for the differences between the three groups remains obscure.

### CONCLUSIONS

1. The secretion of gastric juice in patients with benign gastric ulcer is apparently continuous; although the secretion of hydrochloric acid is not continuous.

2. The volume of secretion and output of acid are usually higher during the first half of the night than during the last half.

3. Individual variations exist. However, patients with a low volume and secretion of acid in one night, in the majority of instances, produce a low volume and acidity on successive nights; a similar constancy exists in patients with a high secretory rate.

4. The rate of gastric secretion is not constant, varying spontaneously from hour to hour in the same individual.

5. The volume, concentration and output of acid in the fasting nocturnal gastric secretion are lower in patients with benign gastric ulcer than in patients with duodenal ulcer.

6. There is no significant difference in the average volume secreted by patients with benign gastric ulcer and normal individuals; however, the concentration of free hydrochloric acid and output of acid are lower in patients with gastric ulcer.

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# CASE REPORTS

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## A CASE OF CHRONIC NEPHRITIS IN CHILDHOOD WITH LATER DEVELOPMENT OF SEVERE HYPERTENSION; RENAL BIOPSY \*

By EARL I. MULMED, M.D., ARCHIE H. BAGGENSTOSS, M.D., and HOWARD B. BURCHELL, M.D., *Rochester, Minnesota*

WHEN physical examination reveals markedly increased arterial pressure, determination of the rôle of the kidneys in the causation of this symptom often presents a difficult problem.

The question may arise as to whether hypertension of the essential type could occur independently in a case in which evidence of past or latent chronic glomerulonephritis is found. Recently we had the opportunity of studying the histologic appearance of the kidneys and of the arterioles of the skeletal muscles in a case in which the clinical picture was that of severe essential hypertension and in which an established history of chronic glomerulonephritis in childhood was obtained. The unusual feature of the case was the discovery of vascular changes consistent with the clinical appearance of primary hypertension and the almost total absence of chronic glomerular lesions.

### CASE REPORT

The patient, a white man, 29 years of age, registered at the Mayo Clinic on May 27, 1946. His main complaint was of high blood pressure and it was his wish that sympathectomy be considered in treatment. He was an intelligent lawyer and had acquired considerable knowledge of his disease from his brother, a physician, and various internists who had treated him.

At nine years of age he had been a patient of Dr. C. Anderson Aldrich and Dr. Aldrich gave us the following facts. The patient was first examined by Dr. Aldrich in a pediatric clinic in April, 1926, when albuminuria and hematuria both graded 3 +, on a basis of 1 to 4 (in which 1 represents the mildest and 4, the most severe condition), and slight edema were noted. The blood pressure was normal and laboratory study of the blood revealed the following: nonprotein nitrogen, 96 mg. per 100 c.c. of serum; urea, 140 mg.; urea nitrogen, 70 mg.; creatinine, 1.8 mg. per 100 c.c. of blood. Gross albuminuria and hematuria continued to be present for six weeks after which the hematuria disappeared but the albuminuria, graded 2 to 4, continued to be found on approximately weekly examinations for the next year. He was seen frequently in 1927 and 1928 during which time a great deal of albumin, red blood cells (occasionally) and numerous casts were found in the urine. Similar observations were made on occasional examination of the patient in 1929 and 1930. He was examined once in the years 1930, 1932 and 1935, when albuminuria was graded 4 + but the chemical composition of the blood and blood pressure were normal. On one occasion in 1930 the blood pressure was found to be 144 mm. of mercury systolic and 72 mm., diastolic (figure 1).

\* Received for publication March 24, 1947.

In 1936 when the patient was 19 years of age he was found to have hypertension during routine examination of the new students entering a university. His blood pressure was found to be 210/120. Later the average blood pressure was 180/110.

In 1936 he was thoroughly examined elsewhere and carefully maintained treatment with thiocyanate was continued for the next 10 years until approximately six months before admission. His systolic blood pressure varied between 160 and 180 mm. on this medication. The diastolic pressures during this period are unknown to us.

Six months prior to admission he began to note occasional mild frontal headaches which usually occurred one to two hours after he arose in the morning or early in the afternoon.

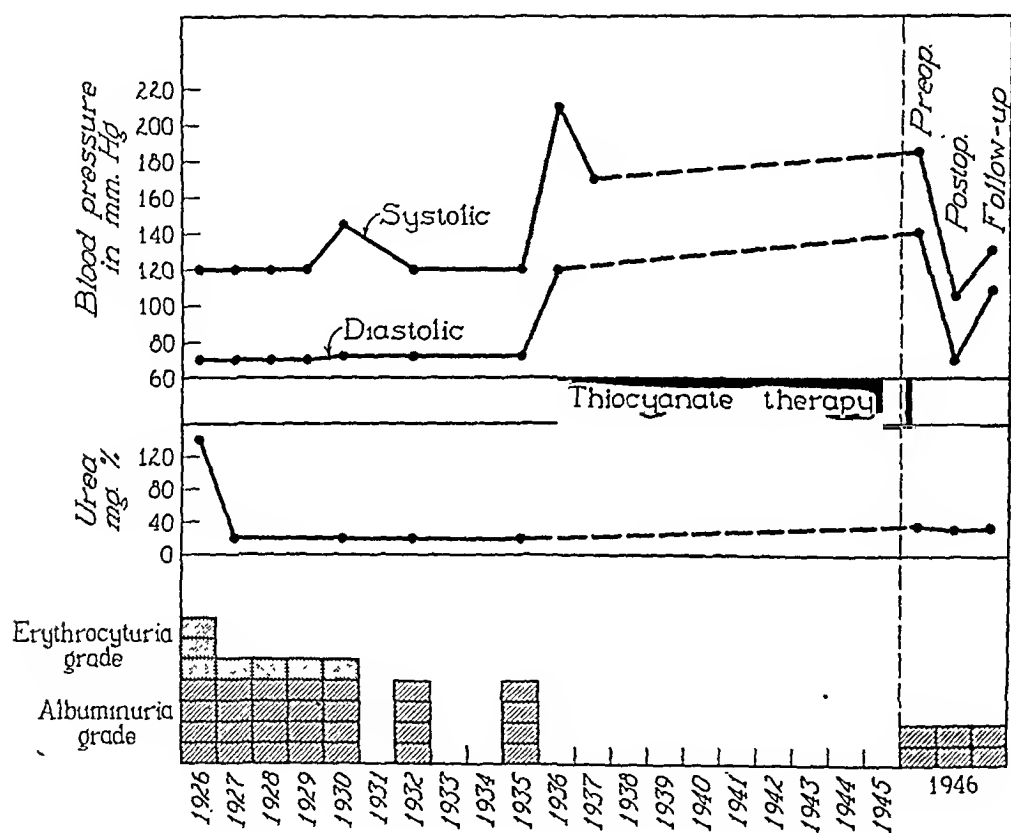


FIG. 1. Summary of findings in a 20 year period of observation.

His past history, aside from the information given herein, and family history were noncontributory.

General physical examination gave negative results except for the finding of hypertension. Clinical examination of the heart revealed that it was normal. The blood pressure was determined hourly for 24 hours; it ranged between 160 and 210 mm. systolic and 116 and 160 mm. diastolic. After administration of sodium amytal, the blood pressure dropped to as low as 150 mm. systolic and 115 mm. diastolic (figure 2). When the cold pressor test was given a rise of 28 mm. in systolic and 10 mm. in diastolic pressure occurred when the patient was in the recumbent position and when he stood no change in the systolic pressure and a rise of 12 mm. in the diastolic pressure were noted.



Examination of the fundi showed hypertensive narrowing, grade 2, with vasospastic constrictions, grade 2 to 2+, of the retinal arterioles. Minimal evidence of sclerosis was found. Cotton-wool patches were numerous and a few small flame-shaped areas of hemorrhagic material were noted in both fundi and a mixture of hemorrhagic material and exudate was observed in the left superior temporal area. Dr. Henry P. Wagener was of the opinion that the fundoscopic picture was that of acute hypertensive retinopathy with little or no sclerosis and that in the presence of hypertension of this duration it was more indicative of glomerulonephritis than of primary essential hypertension.

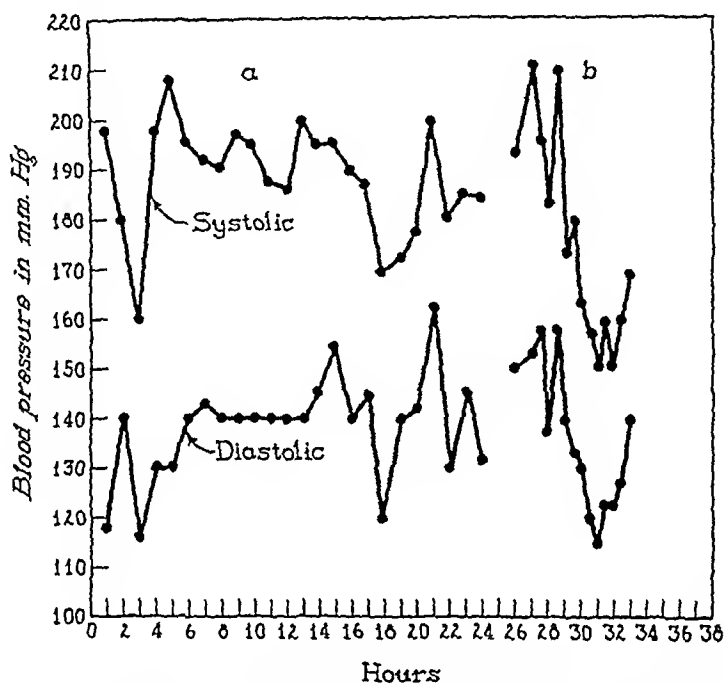


FIG. 2. Preoperative studies. (a) Blood pressures determined at hourly intervals for 24 hours. (b) Blood pressures during the amytal test.

TABLE I  
Preoperative, Postoperative and Follow-Up Laboratory Findings

	Preoperative Values, June 7, 1946	Postoperative Values, July 18, 1946	Follow-up Values, October 10, 1946
Urea*	36 mg.	32 mg.	34 mg.
Creatinine*		1.2 mg.	
Sulfate†	4.6 mg.	5.1 mg.	4.8 mg.
Urea clearance‡	39.9 c.c.	139.4 c.c.	55.5 c.c.
Volume of urine per minute	1.8 c.c.	5.1 c.c.	1.53 c.c.
Sulfate clearance‡		75.9 c.c.	37.3 c.c.
Calcium†	9.8 mg.		
Phosphorus†	2.8 mg.		
Protein†	7.7 gm.		
A-G ratio	2.0/1.0		
Protein in 24 hr. urine specimen§	0.18-0.35 gm.		0.22 gm.

\* Per 100 c.c. of blood.

† Per 100 c.c. of serum.

‡ Of blood per minute.

§ Per 100 c.c. of urine.

On routine urinalysis specific gravity ranged from 1.011 to 1.020, albumin was graded 2 and microscopic examination gave negative results. The urine concentration test showed that the maximal specific gravity was 1.027. The concentration of hemoglobin was 15.3 gm. per 100 c.c. of blood. The erythrocyte count was 4,980,000 per cubic millimeter and the leukocytes numbered 8,700 per cubic millimeter. Results of the flocculation test for syphilis were negative. The chemical constituents of the blood were normal and in addition the results of the urea clearance test and protein content of the urine were within normal range (table 1).

Roentgenologic examination of the thorax gave negative results and the heart was normal in size. Excretory urograms showed no evidence of small or contracted kidneys. The electrocardiographic findings were normal.

While being allowed moderate activity the patient was given potassium thiocyanate. The concentration was maintained at approximately 8 mg. per 100 c.c. of blood and his blood pressure averaged 190 mm. systolic and 130 mm. diastolic.

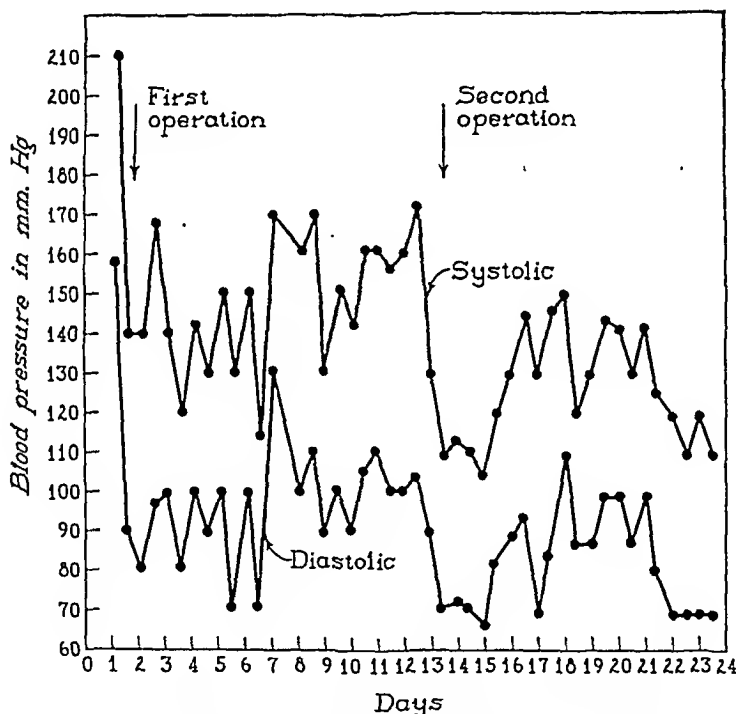


FIG. 3. Blood pressures after extensive right and left supradiaphragmatic and infradiaphragmatic sympathectomy.

In summary, from the findings during the period of observation it seemed an undoubted fact that the clinical diagnosis should be chronic glomerulonephritis of long standing which had probably been present since the patient's childhood. In recent years, however, he had severe hypertension without evidence of progressive renal disease or impairment of renal function. It was thought that, because of the very slight, if any, clinically apparent renal involvement and the acute progressive vasospastic hypertension which was present, it would be justifiable, if the patient understood the possibilities of improvement, to carry out extensive thoracolumbar sympathectomy.

On June 24, 1946, and July 6, 1946, Dr. J. Grafton Love, whose interest and coöperation greatly facilitated the making of this study, carried out extensive supradiaphragmatic and infradiaphragmatic sympathectomy on the right and left sides.

respectively, and removal of specimens from the kidneys and oblique muscle of the abdominal wall for diagnosis. The record of the blood pressures after each of these procedures is shown in figure 3.



FIG. 4. Normal glomeruli of left kidney. (Hematoxylin and eosin;  $\times 60$ .)

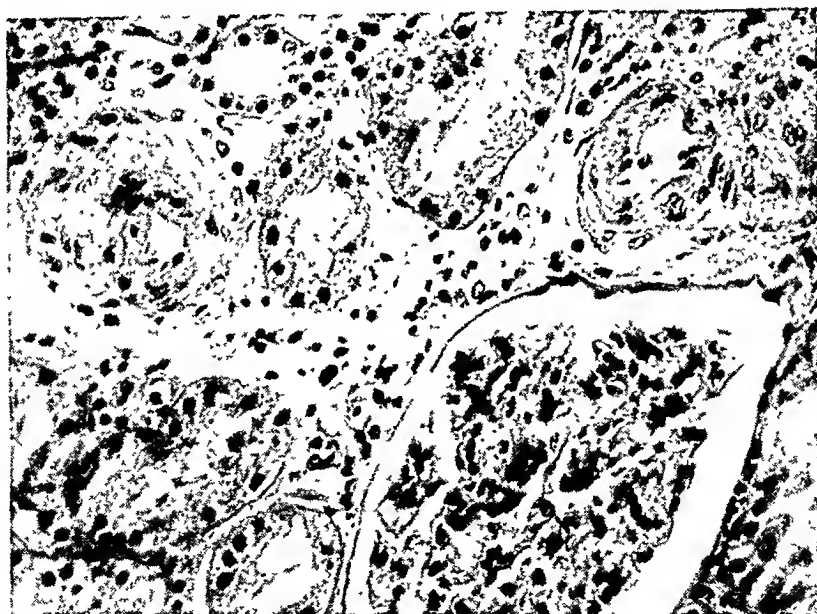


FIG. 5. Left kidney. Slight thickening of capillary basement membranes. Intimal proliferation and hyalinization of arterioles. (Hematoxylin and eosin;  $\times 400$ .)

The patient's convalescence was uneventful and he was dismissed from the hospital on July 17, 1946. Studies of the blood pressure for a controlled period after that date revealed a systolic pressure of between 80 and 130 mm. and a diastolic pressure of between 52 and 90 mm. The lower levels were noted when the patient was standing. Severe orthostatic tachycardia was present. The cold pressor test

administered with the patient in the recumbent position showed an elevation of only 12 mm. in the systolic pressure and 8 mm. in the diastolic. When he was standing a rise of 12 mm. in the systolic and 16 mm. in the diastolic pressure was noted.

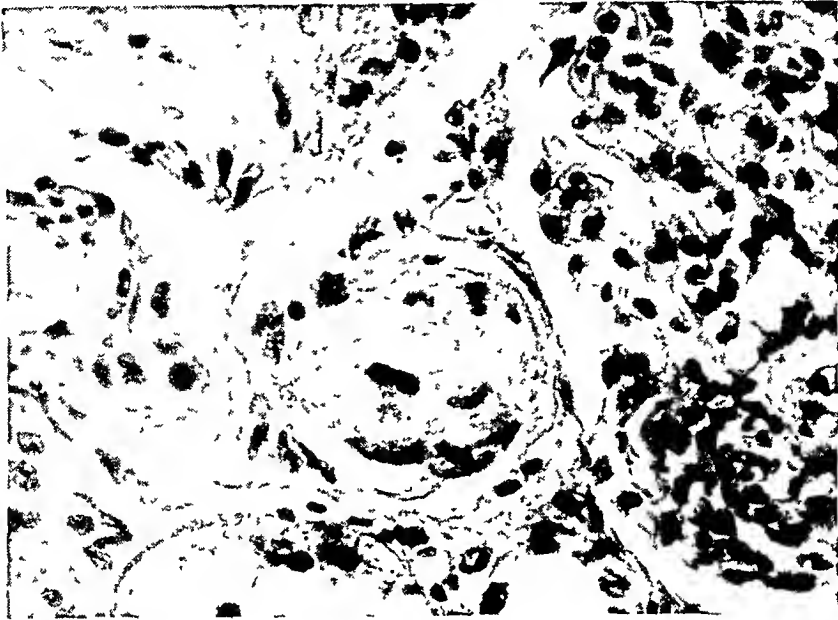


FIG. 6. Left kidney. Intimal proliferation and slight hyalinization of arteriole. (Hematoxylin and eosin;  $\times 400$ .)

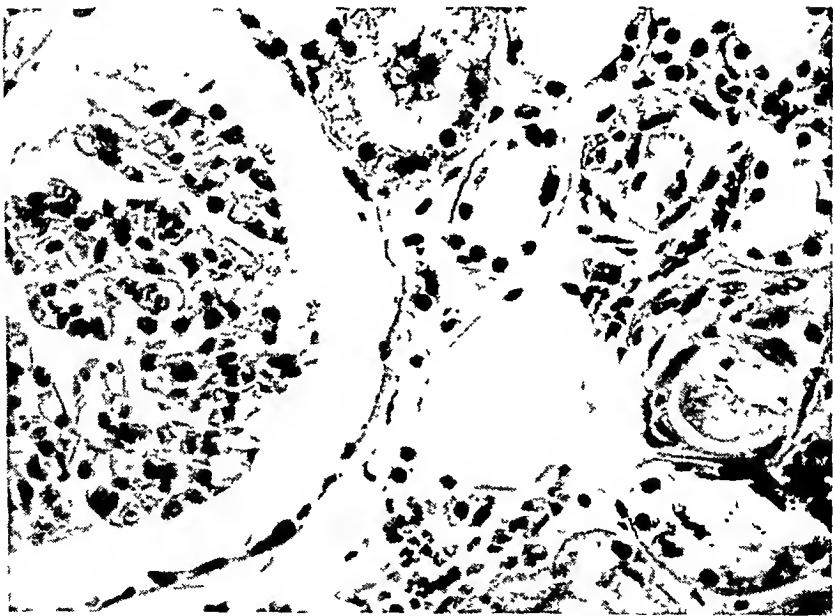


FIG. 7. Right kidney. Intimal hyalinization of arteriole (Hematoxylin and eosin;  $\times 300$ .)

Reexamination of the ocular fundi on July 17, 1946, showed general narrowing, grade 1, of the retinal arterioles and rather minimal chronic sclerosis, grade 1. No localized spastic constrictions were seen. One residual cotton-wool patch was found in each retina and evidence of a previous punctate hemorrhage was seen on the right. Postoperatively spastic activity was markedly decreased; renal function was normal

and the values for the chemical constituents of the blood were within normal range (table 1).

The patient returned for examination in October, 1946, three months after he was dismissed from the hospital. He stated that he felt well except for shortness of breath on standing. This shortness of breath was more pronounced when he stood quietly than when he walked. He was able to walk at a normal rate for one to two miles. He had no headaches. His blood pressure was 150 mm. systolic and 112 mm. diastolic when he was lying down and 118 mm. systolic and 105 mm. diastolic when he was standing. The corresponding pulse rates were 80 and 120 beats per minute. Renal function was normal despite the persistent albuminuria. Results of laboratory studies of the blood were normal (table 1). Funduscopic examination revealed generalized narrowing, grade 1, of the retinal arterioles with minimal sclerosis, chronic hypertensive type, grade 1. No spastic vasoconstrictions were seen. No evidence of retinopathy was found. Small temporal crescents and slight retinal thickening were noted at the upper pole of the right disk.

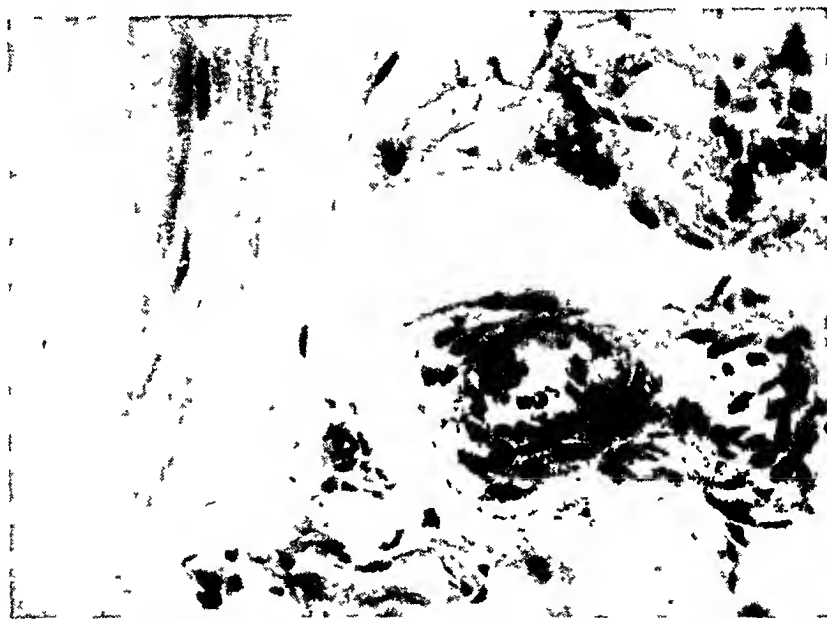


FIG. 8 Oblique muscle of abdominal wall. Slight hypertrophy of the media of small arteries. (Hematoxylin and eosin;  $\times 350$ )

*Pathologic Examination of the Kidneys.* At the time of operation the surgeon described both kidneys as being of normal size and shape. The color and texture were normal and scarring was not observed.

The histologic appearance of the sections of both kidneys was similar and they are described together. Most of the glomeruli appeared normal (figure 4) but occasionally a hyalinized glomerulus was seen. In a few glomeruli slight thickening of the capillary basement membranes was observed (figure 5). Evidence of intimal proliferation and hyalinization of the arterioles, grade 2 (figures 5 to 7), was found. The media of the small arteries and arterioles was somewhat hypertrophied (figures 5 and 6). The histologic picture of the kidney was that observed in cases of essential hypertension of the benign type with no evidence of glomerulonephritis.

Examination of the section of the oblique muscle of the abdominal wall revealed slight hypertrophy of the media in the walls of the small arteries, as well as some intimal proliferation (figure 8). The changes were not as marked as those in the kidney.

## COMMENT

Despite the fact that essential hypertension and chronic glomerulonephritis are distinct diseases, sometimes the clinical picture may be so similar that distinguishing between the two may be difficult. In the presence of evidence of previous glomerulonephritis, the onset of progressive hypertensive disease with arteriolar changes and hypertensive retinitis makes the differential diagnosis even more difficult and sometimes impossible. It is important to know the phase of each disease because, as Wagener and Keith<sup>1</sup> have pointed out, the rapid onset of hypertension often ushers in the terminal phase of chronic glomerulonephritis. The first interesting feature of our case was that the verified history of glomerulonephritis in childhood plus persistent albuminuria for ten years afterward led to a diagnosis of a latent type of chronic glomerulonephritis. The maintenance of good renal function despite the albuminuria and severe hypertension of ten years' duration led us to suspect that the hypertension might not be entirely nephrogenic. The possibility that the severe hypertension had further affected the kidneys and that the acute angiospastic retinopathy represented the onset of terminal failure was of considerable concern to us. The findings on renal biopsy were those of primary or essential hypertension and we were probably justified in assuming that the two different disease processes were present.

The inevitable question of the pathogenesis of the hypertension which has remained unanswered through the years again arises. Johnson<sup>2</sup> in 1868 associated the hypertrophy of the muscular walls of the small renal arteries with the advanced stages of all the forms of chronic Bright's disease and regarded the kidney as the primary site. Gull and Sutton<sup>3</sup> in 1872 found the arterioles throughout the body more or less altered in cases in which the contracted kidney of chronic Bright's disease was found. They termed the alteration "hyalin-fibroid" change and observed that the changes in one case differed from those in another. They suggested that "these changes are or may be independent of renal disease and that the renal change in chronic Bright's disease with contracted kidney, when present, is but a part of a general morbid condition. These two hypotheses, suggested approximately 75 years ago, concerning the vascular changes still represent the divergent views as to the pathogenesis of hypertension: (1) that it is secondary to renal disease and (2) that the renal changes are but a part of a diffuse arteriolar disease which in turn is associated with the disease, essential hypertension.

In 1934 the hypothesis of primary renal origin was brought to the fore by Goldblatt and his associates<sup>4</sup> who produced experimental hypertension through renal ischemia by clamping the renal artery. Page<sup>5</sup> in 1939 produced severe arterial hypertension by means of perinephritis induced with cellophane. In 1937 Moritz and Oldt<sup>6</sup> concluded from objective examination of the arterioles in all parts of the body in 100 control cases and 100 cases of chronic hypertension that "the only significant site of arteriolar sclerosis so far as the causation of hypertension is concerned is the kidney."

In more recent years an attempt has been made to study, not only the cases of advanced hypertension and those of long duration, but cases of a less severe type of hypertension and those in which the condition was amenable to surgical treatment. Castleman and Smithwick<sup>7</sup> in 1943 performed renal biopsy in 100 cases of hypertension in the course of splanchnic resection. In their work the

outstanding finding was "that the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing the hypertension." This led them to think that in many cases "some other functional factor or factors exist which are primarily responsible for the hypertensive state and which precede the appearance of renal vascular disease." This view or approach to the subject of essential hypertension is the more acceptable from the pathologic standpoint. Wagener and Keith, in their discussion of diffuse arteriolar disease, agreed with those who thought that it is not of primary renal origin.

The second interesting feature of our case is that the changes in the arterioles of the muscle were not as extensive as those found in the kidneys. This finding is in keeping with the preliminary observations of Castleman and Smithwick that the peripheral vascular disease develops after the vascular changes due to renal disease. Kernohan and others<sup>8</sup> in 1929 pointed out that the presence of a lesion in the arterioles of muscles is indicative of diffuse vascular disease and knowledge of the degree of change may help to determine the diagnosis and prognosis in an individual case.

The third feature was the absence of any evidence of chronic glomerulonephritis in the renal specimens. Bell<sup>9</sup> presented six cases of chronic glomerulonephritis in which death was caused by another disease before marked renal insufficiency had developed. He stated, "These cases are of particular interest since little is known of the structure of the kidneys in the interval between the acute attack and the development of renal insufficiency." In the cases he presented some evidence of renal injury was present in all but renal function was not seriously impaired. He described the microscopic findings in one case and stated that those in the others were similar. His description follows: "About 10 per cent of the glomeruli are hyaline, and there is atrophy of their associated tubules. Practically all of the other glomeruli present a similar appearance. They are slightly enlarged and their lobulations are distinct. Under higher magnification the lobules show solid central portions with small peripherally situated capillaries. There is some increase of endothelial cells but the capillaries are not markedly constricted. The peripheral capillary basement membranes are not thickened. Glomerular filtration is evidently fairly good since there is no atrophy of the tubules associated with these glomeruli." These findings are essentially the same as those of writers on the subject of latent glomerulonephritis. The changes observed by Bell were not found in our case.

In 1925 Dawson<sup>10</sup> described a case of hypertension in which he had observed the patient, a girl, 22 years old, for three years. At times a trace of albumin and a few hyaline casts had been found in the urine. The patient had had a severe attack of scarlet fever in childhood. Her primary complaint was of a migraine type headache which she began to have at the age of eleven. A suggestion was made that she had slowly progressive interstitial nephritis. At operation the kidneys were decapsulated and portions of the kidneys were secured for examination. Examination of the sections showed the following: "(1) the most marked feature was hypertrophy of the tunica media of the larger arteries; (2) slight changes including some fatty degeneration of the intima of the smaller arteries; (3) patches of partial atrophy of tubules due to infiltration by small round cells

(early fibrous changes). Changes characteristic of interstitial nephritis were absent." Report of examination of these sections was made by Professor Turnbull of the London Hospital.

The great similarity between this case and the one herein reported lies in the lack of those findings in the kidney which are usually associated with chronic glomerulonephritis. To date, the kidney in the asymptomatic latent phase of chronic glomerulonephritis has not been sufficiently described. One is led to speculate that the kidney in this phase in some instances may be essentially normal in structure by present standards, yet so far as function is concerned persistent albuminuria may be present.

### SUMMARY

A case of hypertension in a white man, 29 years old, is reported. The patient had had glomerulonephritis at nine years of age which clinically had progressed to latent chronic glomerulonephritis. At the age of 19 hypertension developed. Renal function remained good throughout the course of both diseases. Bilateral sympathectomy was performed and the result was satisfactory. Biopsy of the kidney and muscle confirmed the fact that diffuse arteriolar disease was present, but no evidence of chronic glomerulonephritis was observed.

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## PSYCHOSOMATIC ASPECTS OF HEART DISEASE: ANXIETY HYSTERIA IN A PATIENT WITH PATENT DUCTUS ARTERIOSUS \*

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Not long ago Oille<sup>1</sup> said, "Almost 60 per cent of the patients who consult a cardiac specialist are suffering either from an exaggerated or wholly unnecessary anxiety about their hearts, arising from suggestion and not based on reason." Nellis<sup>2</sup> stated that no layman he had ever questioned had noticed a relationship between emotional stress and heart action; even medical students failed to appreciate it. Yet this relationship is so familiar to physicians that they forget its clinical implications. These statements immediately make it clear that a doctor often has to look beyond the cardiovascular system into the psyche in order to treat and understand the person who presents himself with a cardiac complaint.

It has long been accepted that the heart is the traditional seat of the emotions and thus acts as the focal point of anxiety. Anxiety neurosis is probably the most frequent disorder of civilized life.<sup>3</sup> It is also well known that anxiety produces such disturbances of cardiac function as palpitation, arrhythmia, tachycardia, and elevation of the blood pressure. With the onset of cardiac symptoms, attention is directed to the heart. This sets the basis for doubting the integrity of the heart that leads to a psychic reaction which seems to be more violent and profound than is the case with any of the other internal organs.<sup>4</sup> This is understandable, because the average layman still associates heart disease with the idea of sudden and unforeseen death. Thus the importance of the heart in the "mind's eye" is incalculable.

Weiss<sup>5</sup> has pointed out that the majority of patients having symptoms referred to the region of the heart show no evidence of organic heart disease. Even though organic disease be present, it may play no part in the illness. Neuhof<sup>6</sup> points out that patients with heart disease may get along fairly comfortably until some psychic disturbance initiates symptoms from which it may take a long time to recover. ~~All too often~~ we as physicians are directly or indirectly responsible for crippling symptoms on an emotional basis, even though the patient may have organic heart disease which is causing few or no symptoms. Any feelings of uncertainty about the function of the heart, arising in the patient's mind or transmitted from the doctor, may start the chain of symptoms. The statement of the physician that "you have a slight murmur" or the "heart action is irregular" or the "muscles are weak" or that "you have an athlete's heart" may furnish fuel for the fire.

Frequently the past history reveals the patient to be an emotionally sensitized individual. Conner<sup>6</sup> gives the following four groups of causes that may serve as a precipitating factor in the development of a cardiac neurosis:

1. The statement of some physician or life insurance examiner that the heart shows some abnormality,

\* Received for publication January 20, 1948.

2. The occurrence of some dramatic case of heart disease (such as sudden death among relatives or friends of the patient)
3. The appearance of symptoms calling attention to the heart, and
4. Some profound and protracted emotional disturbance, such as deep grief or prolonged anxiety.

The pernicious practice of attributing symptoms to low blood pressure may kindle the first awareness of the circulation. Individuals may be particularly susceptible after an illness, when there has been a loss of muscle and vasomotor tone with weakness, postural drop in blood pressure, dizziness, and orthostatic tachycardia. Extrasystoles are more prone to occur and are more noticeable to the patient. Bed rest lends itself to introspection, and bodily functions normally unnoticed may reach conscious level.

Since cardiac symptoms may occur in neuroses of all types and even in psychoses, they are only the presenting symptoms of a more fundamental disorder—the individual's inability to handle his personal and environmental problems. The physician limiting his attention to the cardiac symptoms permits the major personality disorder to escape unnoticed and helps to fix the anxiety at a somatic level.<sup>7</sup>

A neurosis presents an attempt on the part of the patient to adjust to a situation that in reality is too much for him to cope with. It accomplishes something for him unconsciously that he is not consciously able to do. It is a substitution, and within this substitution lies the genesis of the patient's symptoms. In this way, as Dunbar<sup>8</sup> points out, ideas and experiences originally accompanied by anxiety but long since forgotten (repressed) can be the cause of disturbances in the cardiovascular system.

Just as neuroses are found in persons with normal hearts, so can they occur in individuals with organic disease. The finding of an organic lesion may blind the physician to the true cause of disability, an underlying emotional disturbance. The association of organic disease and emotional disturbances is not uncommon. Patients with congenital heart disease with murmurs or abnormalities since birth are particularly susceptible, since usually they have been overprotected and fenced in with imposed restrictions and constant reminders of their limitations. Patients with rheumatic heart disease are similarly affected, the long periods of enforced bed rest lowering the threshold of heart consciousness and giving fertile grounds for neurosis. Patients with essential hypertension are notably difficult to evaluate, psychic factors being predominant in this condition. They have been taught to expect headaches, dizziness, etc. As one patient recently said, "I know I am supposed to have these, but I do not."

Adler<sup>9</sup> states that in connection with psychological questions he had always noted that one of the most important reasons for lack of courage in handling problems in life is the existence of an organic burden in childhood. He points out that delicate children differ very much from the healthy in their views of the world, because they suffer from organic deficiencies and defects. Thus, feelings of personal inferiority are greatly intensified in those burdened with physical defects. To be sure, an inferior organ may even become the site of a neurosis, as is demonstrated in the case presented here.

When organic disease is present in an emotionally unstable person, one can expect to find evidence of the neurotic element in the appearance of symptoms

which cannot reasonably be ascribed to the organic disease present. Conner<sup>10</sup> further states that the symptoms are subjective in nature and lie outside the legitimate manifestations of the existing organic disease. When the structure of the disease is severe, the neurotic symptoms, if present, are apt to be relatively unimportant. It is in the milder forms of heart disease, with few or no real organic symptoms, that emotional reactions tend to occupy the foreground and demand serious consideration. This differentiation requires the utmost in skill, judgment, and experience on the part of a physician; how he handles this will largely determine the success or failure in the treatment of the patient. It is important to understand, as Weiss<sup>11</sup> explains, that the neurotic patient who has organic heart disease may add a real burden to the work of his heart, either through constant tension of psychic origin or, more especially, by means of acute episodes of emotional origin. It may hasten a cardiac breakdown which might be indefinitely postponed if there were no psychic stress. Thus, psychic factors may be more important than the physical factors producing incapacitation.

Pain is probably the most frequent subjective sensation accompanying emotional disturbances of the heart.<sup>12</sup> The origin of this kind of pain is usually anxiety. Evidence suggests that it may be due to faulty respiration with limited movement of the diaphragm and increased intercostal movement with accentuation by trauma resulting from impingement of the contracting heart against the intercostal muscles.<sup>15, 16</sup> Lipkin<sup>13</sup> states that the pain usually is located in the outer precordium, especially in the region of the apex, probably because most people believe the heart is located somewhere in the outer part of the left chest. Parkinson<sup>17</sup> has said, "No patient should ever be permitted to speak of left mammary pain as 'pain in the heart,' for it is this symptom more than any other which suggests to him the false and dangerous idea of heart disease." The pain usually is described as "sticking," "burning," "like a stitch," or as a "stabbing." In contrast to the short anginal attacks, it may last hours or even days; and it is not steady, but intermittent. It is often made up of darts and twinges. The intensity changes from moment to moment, and it is not sharply related to exertion but is more often experienced after a period of exertion rather than during exertion. It is not immediately relieved by rest or nitrites.

Dyspnea is also a very common symptom; however, if one asks the patient carefully to describe his "shortness of breath," he learns that the patient has a sense of pressure or weight on the chest. The patient states that he cannot take a deep breath, and the air that he does get in is not enough. This may be accompanied by a sighing type of respiration and even lead to the production of the so-called hyperventilation syndrome. It is here that the hyperventilation test as described by Giebe and Auerbach<sup>14</sup> can be most useful, as it may even completely reproduce the patient's symptoms. The patient may complain of palpitation or "heart consciousness," which usually is manifested by tachycardia, arrhythmia, or both.

Objectively, the presence of a murmur leads to more false diagnoses of cardiac disease than any other single finding. Functional murmurs can be heard in a large number of healthy patients. This type of murmur is usually systolic in time and not associated with enlargement of the heart or great vessels. It is commonly localized, and rarely, if at all, is there any area of transmission. Usually it is located in the pulmonary or mitral areas, is blowing in nature, and varies with change of position and breathing.

If, however, there is any doubt as to the significance of a murmur, it is better not to let the patient be aware of this fact until enough evidence is found to establish the organic status of the heart. A cardiac neurosis often has its nucleus in the indiscreet remark of an examining physician who detects for the first time a systolic murmur at the pulmonic area or apex, which is unaccompanied by other evidence of organic disease.

It is essential properly to weigh the amount of disability due to physical and the amount due to emotional causes. Not infrequently when the differentiation is difficult, the physician may ascribe the disability to organic disease because of the fear of missing the diagnosis or overlooking some condition. It would seem far better to miss the diagnosis in an occasional obscure case than to condemn those with symptoms or findings suggestive of organic heart disease to the fears, uncertainty, and mixed emotions inherent in the cardiac.

Treatment should begin with the very first visit. The physician has to be fully aware not only of what he says but also of his attitude in regard to the total situation. In order to do this effectively, a careful complete history and a thorough, authoritative physical examination is necessary. Laboratory procedures should be done only when indicated. Then a frank discussion should be held with the patient. Great care should be taken not to over-estimate the organic disease when present. If an electrocardiogram or roentgen-ray examination is necessary, the necessity should be explained. If no organic lesion is found, the physician should speak frankly about this and explain how emotional stress can produce physiological responses in the cardiovascular system. If one is in doubt as to the diagnosis and consultation is thought to be needed, this, too, should be explained. The whole object is to reach a positive diagnosis as soon as possible, and then treat accordingly. If the problem is a difficult emotional one, psychiatric help should be sought. If primarily organic, it should be handled accordingly. In some cases, both the organic and psychic problems will demand expert care. Treating the patient as a whole is the only way of handling the situation successfully, and it may prevent the patient from falling into that not too uncommon group of heart diseases produced by the physician.

#### CASE REPORT

Mrs. C., a 39 year old married white female, was admitted to the hospital on January 30, 1947 with a history of being confined to bed for the previous three years because of heart trouble. At the age of fifteen she was said to have had a "heart attack" and was taken to a local hospital, where, during the course of examination, a murmur was found. She was told that this was the cause of her trouble, and that she would have to live a restricted, cautious life. Since then she has had recurrent "heart attacks" characterized by extreme shortness of breath, a sense of suffocation and weight on her chest, palpitation, numbness and tingling in her arms and legs. With her first attack she remained in bed one year, and after an interval of one year she went to bed for seven years. She recovered enough to be up and around for about 12 years. During the previous three years, she had been at complete bed rest, the slightest bit of exertion producing attacks. For two years she had been on a diet of goat's milk and soft food, because of epigastric discomfort occurring one to two hours after eating. Her mother died of a heart attack, and her sister is said to have heart trouble.

Physical examination revealed a thin, anemic, tense, malnourished woman. The blood pressure was 138 mm. Hg systolic and 88 mm. diastolic in the right arm, and

148 mm. Hg systolic and 92 mm. diastolic in the left arm. The temperature was 103° F., pulse 92, and respirations 22. The significant physical findings were as follows: There was a severe pyorrhea of the gums. The teeth were in poor repair, and there was moderate fetor oris. The lungs were clear. The heart size was normal. There was a typical machinery murmur of a patent ductus arteriosus heard in the second left intercostal space; no thrill was palpated. The rhythm was regular, and the rate was 92. Her weight was 96 pounds. The remainder of the physical examination was normal.

Fluoroscopic examination showed the heart to be of normal size. The pulmonary artery segment was normal with no increased pulsations. The electrocardiogram revealed an unimportant degree of left axis deviation. The urine examination was normal. The red cell count was 4.67 million, with 88 per cent hemoglobin. The white cell count was 6,000 with an essentially normal differential. The Kahn was negative. The sedimentation rate fell 7 mm. in one hour.

Hyperventilation reproduced the so-called heart attacks. The symptoms rapidly subsided upon rebreathing carbon dioxide. A diagnosis of severe chronic anxiety hysteria, with hyperventilation attacks was made. Although the patient had organic heart disease due to a patent ductus arteriosus, there was no evidence of impaired cardiac reserve. The patent ductus was incidental to a severe psychoneurosis.

Psychiatric study revealed that the patient was an emotionally unstable person long before her first "heart attack" took place. Her home situation was an unhappy one. She described her father as being "unaffectionate"; "strict"; a "puritan-primitive" kind of man. Her mother was not very demonstrative of her affections. Her parents were not happy themselves.

When only fourteen and a half, she married a man of thirty-nine. When asked why she did this, she said that he was "nice to me"; he was "affectionate"; he was "like a father." A very short time after her marriage, however, she was faced with the reality that he did not love her. This marriage ended in a divorce.

About three months after her marriage, she developed a rash. In spite of negative serological tests on the blood and spinal fluid, she was reminded by her doctor that she still might have syphilis. Actually, the rash turned out to be due to bromides.

One month before her first spell, her father died, and this upset her a great deal. About the same time her sister, who was supposed to have heart disease, had an abortion and "nearly died with it." Just prior to her first "heart attack," she thought, "What a mess the whole situation is." As soon as the diagnosis of a murmur and heart disease was made, a somatic crutch was given to her upon which she focused all her anxiety, and everything soon became "my heart condition."

After a year in bed she began to recover slowly. She realized that she didn't love her husband, but he plagued her constantly and produced many embarrassing situations. The only time she felt safe and secure from him was when she was sick in bed. As his threats became more persistent, she spent more and more time in bed, finally remaining there for seven years!

It is interesting to note that around her seventh year of bed rest, her husband made it clear that he no longer wanted her and would like to have a divorce. With this turn of events, her fears began to disappear, and improvement occurred.

Shortly after this, she met her present husband. As this friendship developed and the threat of her first husband passed, she finally got out of bed. Her friendship with Mr. C. culminated in marriage in February of 1941, shortly after her divorce from her first husband became final. She did not marry Mr. C. for love, but for "practical reasons." He was "nice," "seemed to like me," and "wanted to look after me."

Then a new turn of events began. She had been told by her doctor that she

should never become pregnant, because she would be unable to carry the pregnancy, and she might even die with it.

In December of 1942 she became pregnant. This ended in a therapeutic abortion. One year later in December, she again became pregnant and had a second therapeutic abortion. She never quite recovered from this. Her fear of pregnancy mounted, and this was solved by returning to complete bed rest.

In July 1944, her mother died of a "heart attack." With her mother's death, she gave up all hope. The attacks became more frequent than ever before. She dreamed about her mother constantly and developed a tremendous guilt complex. She felt that she was responsible for her death and should have done a lot of things for her that she had not done while she was alive.

Before coming to the hospital, she asked her physician what possibly could be done for her. She was told frankly that nothing could be done. It was with an attitude of hopelessness that the patient came to the hospital.

Treatment consisted of daily therapeutic interviews with and without hypnosis, occupational and physical therapy, and a high caloric diet supplemented by iron and vitamins. Using these technics, the patient was able to get out of bed after her first interview under hypnosis but had to relearn to walk. With the liberation of her repressed hostilities and a change in outlook of life, she made rapid progress. She gained in weight from 96 pounds to 108 pounds. Her heart rate and temperature became normal. Whereas five months prior to her admission to the hospital she had been taking large amounts of sedatives during the day and night, she was discharged with no sedation. Whereas she entered the hospital in an ambulance, being unable to walk, she left fully ambulatory. Thus, during a five week period, she learned that her trouble was not in her heart literally speaking, but that her major problem was a chronic emotional one.

The patient was seen again a month after her discharge and was happier than she had been in years.

In summary, we find that the patient was born with an inferior organ, her heart. She was emotionally unstable from childhood, having experienced much emotional trauma. At 15 she had her first overt anxiety "heart attack" which drew attention to this organ. Her anxieties were confirmed by doctors when she was told that she had a murmur and would have to spend the rest of her life taking it easy. Then there were the many years of bed rest—11 years in all—with the repeated confirmation by doctors that her trouble lay in her heart. This is an example of the inferior organ being the center of the neurosis. On studying the patient as an individual, she was found to have organic heart disease, but in addition she had been suffering from a severe chronic anxiety hysteria neurosis since age 15. Only by treating her as an individual was she able to express her repressed hostilities, develop a new outlook on life, and then return to a useful existence.

### SUMMARY

A case of long standing anxiety hysteria occurring in a 39 year old patient with patent ductus arteriosus is reported. The emotional influences underlying the illness are studied, and comments are made on the functional aspects of organic heart disease.

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## STREPTOMYCIN TREATMENT OF BACTERIAL ENDOCARDITIS DUE TO *STREPTOCOCCUS VIRIDANS*; REPORT OF TWO CASES \*

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THE precise place of streptomycin in the treatment of bacterial endocarditis has yet to be definitely established. It has been proposed<sup>1</sup> as the drug of choice in cases caused by gram-negative bacilli susceptible, at least in vitro, to streptomycin. It must also be considered, however, in the small fraction of cases due to nonhemolytic streptococci in which the organism is initially resistant to penicillin, as well as the still smaller fraction, where penicillin resistance develops during therapy.

Relatively few reports<sup>1, 2, 3, 4</sup> have appeared concerning the use of streptomycin in bacterial endocarditis, and the percentage of these cases due to penicillin resistant *Streptococcus viridans* has been low. The following two cases are considered worthy of addition to the literature for two reasons: they illustrate apparent cure of such infections without significant toxic effects; and they demonstrate the balance necessary between clinical judgment and the utilization of in vitro tests of streptomycin sensitivity in determining the course of therapy.

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## CASE REPORTS

*Case 1.* A 20 year old white merchant seaman was admitted to the U. S. Marine Hospital, Staten Island, N. Y., on May 11, 1946, complaining of pain in his joints. Except for a questionable episode of rheumatic fever at the age of nine, the patient had been well until two years prior to admission, when he began to note intermittently, migratory polyarthritides and fever. In January 1945, while under observation in another hospital following a blow to his head, he had an apparently typical attack of rheumatic fever, and was told by his physician that he had a heart murmur. After three months' hospitalization, he remained asymptomatic until May 9, 1946, when polyarthritides of increasing severity, and marked fatigue were noted. Chills and fever were first observed by the patient on the morning of admission.

The only positive findings disclosed on initial physical examination were a blood pressure of 155 systolic, 0 diastolic, temperature 101° F., pulsating neck veins, and harsh systolic and diastolic murmurs over the aortic and mitral regions of the heart.

The red cell count was 5,100,000, with a hemoglobin of 16 grams. The white cell count was 7,200 with a differential count within normal limits. Complete examination of the urine was negative. Mazzini and Kahn tests were negative. Roentgenogram of the chest was normal. The electrocardiogram showed a PR interval of 0.20, with elevated ST<sub>2</sub> and ST<sub>3</sub> segments. Sedimentation rate (Cutler method) was 17 mm. in one hour.

Despite intensive salicylate therapy, joint pains and weakness persisted, while the temperature daily spiked to 101° to 102° F. On June 5, a subungual splinter hemorrhage on the index finger of the right hand, a typical Osler node on the fifth finger of the left hand, and several petechiae on the left great toe were observed. Five days later, conjunctival petechiae appeared, and the spleen became palpable. The white cell count rose to 16,700 with 80 per cent neutrophils, 14 per cent lymphocytes and 5 per cent mononuclears. Sedimentation rate was found to be 28 mm. in one hour.

The blood was cultured on June 5, 6 and 10, and the presence of typical alpha hemolytic streptococci (*Streptococcus viridans*) was disclosed in each specimen. Initially the cultures showed 30 colonies per c.c. of blood. The organism appeared to be sensitive to penicillin in a range from 0.07 to 0.15 unit per c.c., and treatment with penicillin was begun, giving 160,000 units intramuscularly every two hours. On June 11, however, a report was received that some of the organisms first cultured were continuing to grow in penicillin concentrations of 2.0 units per c.c. It was eventually determined that these organisms were not completely inhibited even in concentrations of 10.0 units per c.c. Penicillin was thus discontinued after 10 doses had been given, and streptomycin was begun, 0.25 gram being administered intramuscularly every three hours.

On June 12, cultures showed two colonies of *Streptococcus viridans* per 5 c. c. of blood. These organisms were markedly inhibited by four units of streptomycin per c.c., and completely inhibited in concentrations of 8 units per c.c. Serum streptomycin levels on June 14 were found to be 30 units per c.c. after one hour, and 20 units per c.c. two hours and 45 minutes after injection of 0.25 gram. On June 15, after 10 grams of streptomycin had been given, the dosage was increased to 0.3 gram every three hours. Blood culture was negative on June 17, and repeated cultures continued so throughout the remainder of hospitalization. Serum streptomycin levels on June 20 were 40 units per c.c. after one hour, and 20 units per c.c. three hours after injection of 0.3 gram.

Marked clinical improvement was noted 24 hours after beginning streptomycin therapy. The patient became afebrile, and rapidly regained a sense of well being, which he maintained. Subsequently, repeated white cell counts and sedimentation rates were within normal limits. Except for transient urticaria, first noted on June 21, and relieved by the use of benadryl, no toxic effects of streptomycin were observed.



Streptomycin was discontinued on July 6, after a total dosage of 58 grams had been given. Twelve consecutive negative blood cultures were obtained, and the patient was discharged on August 20, 1946, apparently cured.

Repeated blood cultures in January, 1947 and again in July, 1947 were negative and the patient remained clinically well and active.

*Case 2.* A 29 year old white male factory worker and World War II veteran was admitted to the U. S. Marine Hospital, Staten Island, N. Y. on December 14, 1946, complaining of pain in his left upper abdomen. The patient had had rheumatic fever at the age of 13, but was otherwise well until two months prior to admission, when he began to note weakness, anorexia and weight loss, following a brief febrile illness described by him as influenza. One month later intermittent short attacks of left upper quadrant abdominal pain began, accentuated by deep breathing. During the week preceding admission, this pain became relatively constant. In this interval too, the patient noted chills and fever, and transitory red spots on the palms of both hands. Total weight loss reached 20 pounds, and the patient was told by his private physician that his hemoglobin was 58 per cent.

Physical examination on admission revealed an acutely ill, pale, anxious young white male with a blood pressure of 122 systolic and 62 diastolic, temperature 100° F., and pulse 110. The lungs were clear to percussion and auscultation. The heart was not enlarged; a soft blowing systolic murmur was heard over the apical region. The spleen was not definitely palpated, but marked tenderness was evident on pressure over the left upper quadrant of the abdomen. A small tender ecchymotic area was present in the left palm. No other significant findings were disclosed.

The red cell count was 3,700,000 with a hemoglobin of 12 grams. Differential white cell count was within normal limits. Initial urinalysis was negative, but the following day showed 12 to 15 red blood cells on microscopic examination. Mazzini and Kahn tests were negative. Combined fluoroscopy and radiography of the chest showed some prominence of the left ventricular segment of the heart, with expansile pulsations of the aorta; the lung fields were clear.

On December 15 a blood culture showed the presence of typical *Streptococci viridans*. Pending the results of sensitivity tests of this organism, penicillin therapy was begun on December 16, giving 50,000 units intramuscularly every two hours. Sulfadiazine and sulfathiazole were also simultaneously begun, but were discontinued the following day, after 10 grams of each had been given. At that time, conjunctival petechiae, a small left retinal hemorrhage, and a loud systolic murmur at the base of the heart were first observed. The patient's temperature fluctuated between 99 and 101° F. until December 19, when it fell to normal. Meanwhile, culture of a blood specimen obtained on December 16 was also reported to show *Streptococcus viridans*. On December 20 a report was received that these organisms were resistant to at least five units of penicillin per c.c., but were completely inhibited by 16 units of streptomycin per c.c. Penicillin was thus discontinued after 2,400,000 units had been given, and streptomycin was begun, 0.5 gram being administered intramuscularly every three hours.

Blood culture on December 24 was negative, and frequently repeated cultures continued so throughout the remainder of hospitalization. Serum streptomycin concentrations from two and one-half to five times that required to inhibit the organism in vitro were obtained during therapy, reaching levels on December 26 and January 12 of 40 and 80 units per c.c., respectively, two and three-quarter hours after injection of 0.5 gram of streptomycin.

On January 2, 1947 urinalysis was negative, white cell count was 15,000 and the sedimentation rate was 28 mm. in one hour. By February 19, however, the white cell count and sedimentation rate returned to normal limits. The patient rapidly regained his strength and appetite, along with complete subsidence of abdominal pain

and tenderness, but he began to complain of dizziness on motion two days after beginning streptomycin therapy. Streptomycin was discontinued on January 20, after a total of 123.5 grams had been given. No further signs of toxicity were observed, and the patient became ambulatory without difficulty. A positive Romberg sign was elicited on February 6, and this persisted until the patient was discharged on March 6, 1947, but he remained otherwise clinically well.

### DISCUSSION

There is considerable evidence<sup>5, 6, 7</sup> that at present penicillin is the drug of choice in the treatment of bacterial endocarditis due to *Streptococcus viridans*. In two of the largest series<sup>5, 6</sup> of cases of subacute bacterial endocarditis reported, this organism was found to be sensitive to penicillin in a range from 0.008 to 0.28 unit per c.c. There are, however, a small group of cases of extremely high in vitro resistance to penicillin. In that portion of these cases in which the organism is susceptible in vitro to streptomycin, it seems reasonable to attempt prolonged and intensive streptomycin therapy.

In treating cases of this disease with penicillin, it has been recommended<sup>7</sup> that enough penicillin be employed to obtain a blood level at least five to 10 times the minimal amount effective in vitro. Dawson and Hunter<sup>5</sup> found that the serum level of penicillin could be predicted with reasonable accuracy from the daily dose of penicillin. Thus 200,000 units daily, administered by constant intramuscular drip, produced an average serum level of 0.07 unit per c.c.; 1,000,000 units produced a level of 0.56 unit per c.c.; and 10,000,000 units produced a level of 6.6 units per c.c. In both cases reported here, the organisms were unusually resistant to penicillin, and it was felt impossible to obtain adequate blood levels of this drug. Recently, however, Boger et al.<sup>8</sup> found that with the aid of caronamide it was possible to give 4,000,000 units of penicillin daily by intermittent intramuscular injection, and yet obtain plasma concentrations of 30 to 60 units of penicillin per c.c.

In the cases of this report, large doses of streptomycin were employed from the beginning of treatment with this antibiotic. This was felt to be particularly important, because of the marked tendency of organisms to develop resistance to streptomycin. Transitory urticaria, and possibly permanent but mild vestibular dysfunction were noted as toxic effects of this therapy, while no other serious toxic manifestations<sup>9</sup> of streptomycin administration were observed. Audiometric and vestibular function tests were unfortunately not done, but it is recommended that they be carried out in any similar future cases.

Although careful bacteriologic control and adequate in vitro tests of streptomycin sensitivity are extremely important, the outcome of therapy cannot always be predicted from the results of these tests. In the first case reported here, 8 units of streptomycin per c.c. were required to completely inhibit the causative organism in vitro, and in the second case, 16 units per c.c. were necessary. These high levels were initially discouraging, but it was felt that a trial of streptomycin therapy was still justified, in view of the poor prognosis of the patients after the failure of penicillin. Actually, the concentration of streptomycin maintained in the blood ranged from two and one-half to five times that required to inhibit in organism in vitro, and clinical cure resulted.

In Hunter's<sup>1</sup> recent report on the use of streptomycin in bacterial endo-

carditis, which included six of his own cases and 12 more supplied to him by Dr. Chester Keefer, only four cases were due to *Streptococcus viridans*. Streptomycin was given for a duration of 14 to 34 days, with a total dosage ranging from 17 to 103 gm. Questionable cure resulted in two cases, while failure occurred in the others.

Of the cases reported earlier by Priest and McGee,<sup>2</sup> only one was due to a typical *Streptococcus viridans*; 2.5 grams of streptomycin were given over a five day period, before the patient died.

Boger et al.<sup>8</sup> reported a case of subacute bacterial endocarditis due to *Streptococcus viridans*, resistant to 69 grams of streptomycin over a 23 days period, but eventually responding to combined intramuscular penicillin and oral caronamide.

A search of the available literature has failed to reveal any other cases of bacterial endocarditis due to typical *Streptococcus viridans*, treated with streptomycin.

### SUMMARY

Streptomycin was successfully used in the treatment of two cases of bacterial endocarditis caused by typical *Streptococcus viridans*.

The causative organism was isolated in each case and determined to be relatively insensitive to penicillin in vitro, but sensitive to concentrations of streptomycin that could be, and actually were, clinically attained.

### ADDENDUM

Follow-up study of the patient V. M. (Case 2) 19 months after discharge from the hospital revealed that he had remained clinically well. Residual vestibular dysfunction had subsided. Urinalysis, complete blood count and electrocardiogram were within normal limits. Roentgenogram of the chest showed no significant change in comparison with previous films. Three blood cultures were negative.

The author wishes to thank Dr. R. H. Smith, Chief of the Medical Service, U. S. Marine Hospital, Staten Island, New York, for his suggestions and helpful advice.

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## TOXICITY OF THIOCYANATES USED IN TREATMENT OF HYPERTENSION \*

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THE purpose of this article is to describe the toxic effects of thiocyanate as used in the treatment of hypertension, and to report a fatal case of thiocyanate poisoning.

### HISTORY AND GENERAL USAGE

The popularity of thiocyanate (SCN) treatment for hypertension has fluctuated over a period of years. The drug was first studied from a pharmacological standpoint in 1857 by Claude Bernard, but it was not until 1903 that Pauli made use of its hypotensive properties in clinical medicine. In 1925, Westphal commented on its toxic effects. In 1929, the Council on Pharmacy and Chemistry of the American Medical Association refused to accept the Elixir and Tablets of Potassium Thiocyanate for inclusion in the New and Non-official Remedies, because of their toxic qualities.<sup>1</sup> Since that time, however, there has been a resurgence of its use, and several fatal and non-fatal cases of poisoning have been reported. Recently, two new proprietaries which contain thiocyanate, "Thiocara" and "Hypersed," have appeared on the market.

In hypertension, thiocyanate reduces the systolic and diastolic blood pressures by 60 and 40 mm. respectively, is effective against headache, and may produce a feeling of general well-being.<sup>22, 23, 24</sup> The drug is given by mouth in 0.2 gram doses sufficient to maintain a blood level of from 5 to 14 mg. per cent. Weekly blood assays are made, and the patient closely observed for signs of toxicity, particularly a maculopapular eruption and toxic psychosis.

### CLINICAL STUDIES

Goldring and Chasis<sup>3</sup> reported on the toxic effects of thiocyanate in a carefully studied series of 69 cases of essential hypertension, and five cases of glomerulonephritis. Thirteen of the 74 cases showed toxic symptoms. Six of these patients developed a toxic psychosis, and of these, two died. There were three cases of motor aphasia apparently due to the drug.

These authors found that the toxic symptoms, in the order of their appearance, are: muscular fatigue, followed by nausea and vomiting; disorientation, mental confusion, motor aphasia, hallucinations of sight and hearing; in fatal cases progression to delirium, convulsive twitchings and death. They quote the work of Nichols<sup>4</sup> who observed a similar march of objective symptoms in guinea pigs. Nichols postulated a strychnine-like action of thiocyanate because of the muscular irritability, twitchings and convulsions. Russell and Stahl,<sup>5</sup> in discussing their fatal cases who had jerking motions of the extremities, stress the convulsive action of thiocyanate.

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Psychosis is extremely common in intoxication with thiocyanate,<sup>27</sup> almost all fatal cases having been preceded by confusion, hallucinations, delusions and psychomotor agitation. Mental symptoms are therefore very significant from a prognostic point of view. Although only three cases of toxic psychosis who recovered have been reported,<sup>6, 27, 7</sup> internists of wide experience state that mental abnormalities during treatment with thiocyanate are relatively frequent.<sup>8</sup>

Others have described the goitrogenic action of thiocyanate. This effect was first noted in rabbits that were fed a diet of cabbage, which contains cyanide in small quantities. Cyanide is partially detoxified to thiocyanate in lower animals and man.<sup>2</sup> Ingestion of foods of the cabbage family probably accounts for the presence of a blood level of 0.030 to 0.060 mg. per cent of thiocyanate in normal men. In human hypertensives, acute diffuse goiter with pain and myxedema have been reported<sup>9, 10</sup> as well as acute enlargement of an adenomatous nodule of the thyroid and chronic diffuse goiter.<sup>11</sup> Thiocyanate produces goiter by a mechanism similar to that of thiouracil.<sup>28</sup> The goiter similarly responds to administration of thyroid.<sup>21</sup>

Coryza-like symptoms have been noted. The skin manifestations of toxicity include pruritus, a maculopapular eruption<sup>11</sup> and exfoliative dermatitis.<sup>12</sup> A maculopapular eruption is one of the earliest and most common toxic signs.

Acute allergic phenomena from thiocyanate include edema of the glottis and larynx.<sup>13</sup> Friedman's patient,<sup>14</sup> who received 18 grams of thiocyanate in six weeks, developed a skin rash with a high eosinophilia, and died. At autopsy, a Fiedler's myocarditis was found, with nodules the size of rice grains throughout the heart, each nodule consisting of masses of inflammatory cells around areas of liquefaction necrosis, and giant cells and eosinophiles at the periphery.

Thrombophlebitis was a relatively frequent complication of long term thiocyanate therapy in the cases studied by Koffler.<sup>15</sup> Of 40 patients, four developed thrombophlebitis. Friedman reports this complication with even small doses of the drug.

A case of subacute glomerulonephritis who had received a total of 3.31 grams in 11 days was reported as a fatality due to thiocyanate.<sup>16</sup> The patient showed frank hematuria and a typical psychosis, and died in renal failure. Bloody diarrhea has also been reported.<sup>17</sup> A fatal case contributed by Weeks showed a subdural hematoma in the absence of signs of trauma.<sup>18</sup>

Kotte, who studied the effects of thiocyanate on animals and in the clinic, and noted no beneficial results, quotes Davis and Barker, who found that prolonged administration of this drug reduces the blood cholesterol, the serum proteins and the red cell count.<sup>13</sup>

A total of 14 deaths due to this drug have been reported previously.<sup>14</sup> Autopsied cases showed no specific anatomical changes which could be directly attributed to thiocyanate. In the autopsied case of Chasis and Goldring, an unusually high level of drug was demonstrated on chemical analysis of the internal organs. The lung tissue contained 17 mg. per 100 grams of tissue, kidney 15 mg. per cent, liver 14 mg. per cent, heart 9.7 mg. per cent. Analysis of the organs of an individual who had not received thiocyanate yielded 4 mg. per cent in the liver and a trace or none in the other organs.

The following case is the fifteenth fatality:

*Case 2: Fatal Thiocyanate Poisoning.\** A 46 year old pharmacist was admitted to another hospital on August 10, 1945, because of dyspnea, palpitation and sweating, which had lasted for eight hours. He had been well until a year before admission, when he first complained of severe headaches in the frontal and occipital regions. On consulting a doctor, he was told that his blood pressure was "240."

On the first admission, he was severely ill, breathing rapidly, with a pulse of 124 and blood pressure of 260 mm. of mercury systolic and 130 mm. diastolic. The eye grounds showed arteriosclerotic changes, hemorrhages and papilledema. The heart was enlarged to the left, and there was a protodiastolic gallop. There were wheezes throughout both lungs and edema of the ankles. The blood non-protein nitrogen was 38 mg. per cent. An intravenous pyelogram was negative.

A diagnosis of essential hypertension was made. He was proposed for treatment by the Smithwick technic of sympathectomy.

However, six days after admission, he suddenly became unable to speak. At that time, his blood pressure was 270/120. No other signs indicative of a focal lesion in the brain were reported. The aphasia disappeared in three days.

A week later, he was "not considered to be a suitable candidate for sympathectomy, because of the cerebrovascular complications, the high diastolic pressure and a poor response to cold, posture and sedation." He was discharged, and returned to this city.

He then came under the care of another physician, who prescribed Elixir of Potassium Thiocyanate USP, digitalis, mercupurin and a salt-free diet. Dosages are not known. However, he soon became "delirious and unmanageable" and had to be transferred to Bellevue Hospital on September 25, 1945.

On admission, his state of consciousness was clouded, so that he was able to respond poorly, and then only to urgent commands. He could make sounds, but was unable to speak words. The pulse was 116, temperature 101.2° F., and blood pressure 220/120. The right hand and right leg were weaker than the left, and there was a "claw" deformity of the right hand. A rough systolic murmur, suggestive of a friction rub, was heard at the apex. The liver was enlarged. Other physical findings were similar to those of two months previously.

The urine was of low specific gravity and contained protein and casts. The blood urea nitrogen was 37.7 mg. per cent, creatinine 2.5 mg. per cent and thiocyanate 25 mg. per cent. (Normal value 0.030 to 0.060 mg. per cent.)

By the third hospital day, Cheyne-Stokes respiration was noted. There were muscular twitchings throughout the body, with positive Chvostek signs. The signs of Chaddock and Oppenheim were elicited on the right leg. The CO<sub>2</sub> combining power of the blood was within normal limits. Blood chemistry figures (in mg. per cent) were as follows:

TABLE I

Date	SCN	Blood Urea Nitrogen	Creatinine
Sept. 26, 1945	25	57.7	2.5
Sept. 28, 1945	21	39.6	2.8
Oct. 1, 1945	11.1	34.5	3.0
Oct. 2, 1945	Died		

Clinically, his condition grew steadily worse. He went into peripheral vascular collapse and died on the seventh hospital day. Final diagnoses were: (1) Thiocyanate poisoning; (2) essential hypertension; (3) infarction of left internal capsule.

\* *Case 1: Toxic Psychosis Due to SCN* has been reported previously.<sup>27</sup>

A complete autopsy was done. Positive findings included a recent infarct of the cardiac apex, and passive congestion of the liver and spleen. The kidneys weighed 170 and 160 grams respectively. Their capsules stripped easily, but the renal surface showed multiple white scars. Many of the glomeruli were atrophic and hyalinized. The walls of the blood vessels were markedly thickened, with narrowing of their lumina. There was much fibrosis between the tubules. An anatomical diagnosis of arteriolar nephrosclerosis was made.

Examination of the brain\* showed sclerosis of the circle of Willis. Both occipital lobes showed areas of cortical softening, and there was softening of the left caudate nucleus and several softenings in the cerebellum. Microscopically, there was fibrosis and endarteritis of the pia-arachnoid. There were areas of early softening around some of the arterioles with actual necrosis of the brain tissue in places. There were many small areas of hemorrhage in the gray matter. Fat stain showed an increase in fat in the gray matter. These findings are compatible with arteriolar sclerosis and arteriosclerosis, followed by infarction.

#### LABORATORY DATA

The minimum lethal dose of sodium thiocyanate, given in a single dose to healthy guinea pigs, is between 200 and 400 mg. per kilogram of body weight.<sup>4</sup> A proportionate minimum lethal dose for an average size man would be 15 to 30 grams. However, this drug is used on individuals who frequently have impairment of their renal function and therefore an impairment in their ability to excrete the drug. In patients with depressed kidney functions, one may then expect the fatal dosage to be somewhat below 15 grams, provided that the time during which the drug is administered is not taken into account. In the eight cases of fatal poisoning in which the exact dosage is known, the amount of thiocyanate ingested has been 3.31 grams, 8 grams, 9 grams, 12 grams, 15 grams, 15 grams, 18 grams, 25 grams.<sup>16, 3, 19, 5, 3, 20, 14, 17</sup>

Some observers utilize the blood level as a guide to toxicity. Barker (who introduced the determination of thiocyanate in the blood) and his associates felt in 1939 that "no case of severe intoxication appeared at a blood level below 20 mg. per cent."<sup>21</sup> From their experience with about 300 cases, they report that the optimum blood level is between 8 and 14 mg. per cent. Massie, Etheridge and O'Hare found that the optimum level was 5 to 7 mg. per cent.<sup>22</sup>

The blood level would be an accurate indicator of the amount of drug in the body if renal excretion were uniform and rapid. However, Goldring and Chasis found that the average daily excretion of thiocyanate in the urine varied from individual to individual by over 500 per cent; Wald, Lindberg and Barker report a variability of 400 per cent. Peters, using human subjects, and Homer Smith, using dogs, found that the renal clearance is "extremely small and variable, ranging from 0.3 per cent to 2.0 per cent of the filtration rate of thiocyanate." About 90 per cent of blood thiocyanate is available for filtration.<sup>25</sup>

Data on toxicity show a corresponding degree of variability. Two similar cases of hypertensive cardiovascular disease developed a toxic psychosis, one after receiving 24 grams of thiocyanate in 18 days, the other 26 grams in 60 days.<sup>6, 7</sup> The blood level is of secondary value in cases of drug sensitivity. Friedman's case showed a blood concentration of 3.3 mg. per cent when symp-

\* The brain was examined by Dr. L. D. Stevenson, Director of Neuropathology, Bellevue Hospital.

toms were well established. Koffler's first case of thrombophlebitis had a blood level of 6.4 mg. per cent.

Most important of all, deaths have resulted from thiocyanate in cases where the blood level was within what is generally considered the safe range—3.3 mg. per cent, 4.2 mg. per cent, 7.0 mg. per cent.<sup>14, 5, 20</sup> A case of toxic psychosis developed when the blood level was 12 mg. per cent.<sup>7</sup>

The total amount of thiocyanate in the tissues at the first sign of intoxication has been studied by the method of measuring the total urinary output, and subtracting this figure from the quantity of drug administered. In four essential hypertensives so studied, there was a variability of about 600 per cent in the residual drug in the body at the time when toxic symptoms first appeared.<sup>3</sup>

TABLE II

Case	Total Dose at Time of Intoxication, grams	Residual SCN in Body at Time of Intoxication, grams	Daily Dose, grams	Days of Treatment	Fall in B.P. at Time of Intoxication
5	12.7	5.0	0.9	13	No
6	5.9	3.2	0.6	9	No
7	26.6	21.5	1.2	22	Yes
8	9.8	8.5	0.6	15	No

The quantity of thiocyanate in the tissues may also be estimated from the blood level by using the known ratio between plasma volume and the volume of the extracellular tissue fluid. However, in cardiac and renal disease, found so frequently in patients with hypertension, there is a disturbance of this ratio.

Laboratory data, therefore, furnish only a general estimate by which we may regulate thiocyanate dosage. Careful observation of the patient will detect the first sign of toxicity, but by the time that intoxication has appeared, a quantity of drug will have been stored in the body tissues, and the period of intoxication will be prolonged.

### SUMMARY AND CONCLUSIONS

1. A fatal case of intoxication by thiocyanate used in hypertension is reported.
2. A review of the literature shows that the principal toxic reactions from thiocyanate include dermatitis, psychotic symptoms, thyroid enlargement, thrombophlebitis, convulsive twitchings, and death.
3. Because toxic symptoms are frequent, severe, and cannot be satisfactorily predicted by laboratory studies, thiocyanate is to be considered a potentially dangerous drug.

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## MASSIVE PERIRENAL HEMORRHAGE IN PERIARTERITIS NODOSA \*

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PERIARTERITIS nodosa has been described with increasing frequency during the past two decades. It is probable that this apparent increase reflects a wider recognition of the entity both clinically and pathologically. The great diversity of symptoms and pathologic processes characteristic of this disease results from the widespread distribution of the vascular lesions which are responsible for the secondary visceral reactions.

Although the kidney is involved more frequently than other organs,<sup>1</sup> massive perirenal hemorrhage is an unusual complication of periarteritis nodosa. We have been able to find nine such cases reported.<sup>2, 3, 4, 5, 6, 7, 8, 9, 10</sup> In two of these<sup>2, 9</sup> the hemorrhage was bilateral, as in the following case:

### CASE REPORT

A 47 year old white male was admitted to the service of Dr. W. A. Bradshaw at the Presbyterian Hospital on April 11, 1946 complaining of severe epigastric pain of four days' duration. The onset was abrupt following a 10 day period of vague epigastric discomfort. The pain radiated posteriorly and gradually decreased in severity over a period of 10 to 14 hours. During the few days before admission the patient was frequently nauseated, and on several occasions he vomited small amounts of bile stained fluid. The pain was uninfluenced by food, alkalis, or by vomiting.

For 10 years the patient had frequently experienced attacks of "indigestion" which were relieved by alkalis. In addition, he complained of occasional cough, shortness of breath, pain in the chest unrelated to exertion, and swelling of the ankles in the morning.

The physical examination disclosed moderate epigastric tenderness, without rigidity or palpable masses. The pulse was regular at 60 per minute and the heart sounds were normal. The blood pressure was 160 mm. Hg systolic and 85 mm. diastolic. The temperature was normal, and respirations were 24 per minute.

Laboratory studies on admission revealed an acid urine with a faint trace of albumin. The specific gravity was 1.016. The red blood cell count was 3,900,000 per cu. mm.; the hemoglobin content was 11.3 gm./100 c.c. (Haden-Hausser). The white blood cells numbered 4,750 per cu. mm. The non-protein nitrogen and sugar content of the blood were within normal limits. The icterus index was 6 units. Serologic tests for syphilis were negative. The blood amylase was 4 units (Winslow). The sedimentation rate was 32 mm. in 60 minutes (Cutler). A roentgen-ray of the chest showed a moderate increase in trunk markings throughout the midlung field on the right side, and some thickening of the apical pleura on both sides. Radiologic examination of the gastrointestinal tract disclosed considerable spasm of the stomach and a deformity of the duodenum suggestive of ulcer. Cholecystogram disclosed an angular deformity of the gall-bladder which was interpreted as due to pericholecystic adhesions. The cephalin flocculation test was +1. The oral hippuric acid test revealed 1.9 gm./475 c.c. of urine. The electrocardiogram showed a slight slurring of the QRS complex. The basal metabolic rate was +32.

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Repeated blood counts disclosed a continuous slight hypochromic anemia, and normal values for the white cells in the differential count except for 9 per cent eosinophiles on one occasion. Serum agglutination tests for *E. typhosus*, *E. paratyphosus* and *B. abortus* were negative. A test for occult blood in the stool was negative. The results of a gastric analysis were normal.

The patient improved symptomatically on a regimen of frequent soft feedings, alkalis, and sedatives, although he developed a persistent low grade fever and was dyspneic on several occasions. Coarse râles accompanied by prolonged expiration were heard intermittently over both lung fields. He was discharged April 28 with a diagnosis of duodenal ulcer and bronchial asthma.

The patient was readmitted on May 4 complaining of severe epigastric pain, vomiting, and pain in the legs. There was localized epigastric tenderness without rigidity, and a positive bilateral Homan's sign. The patellar reflexes were absent.

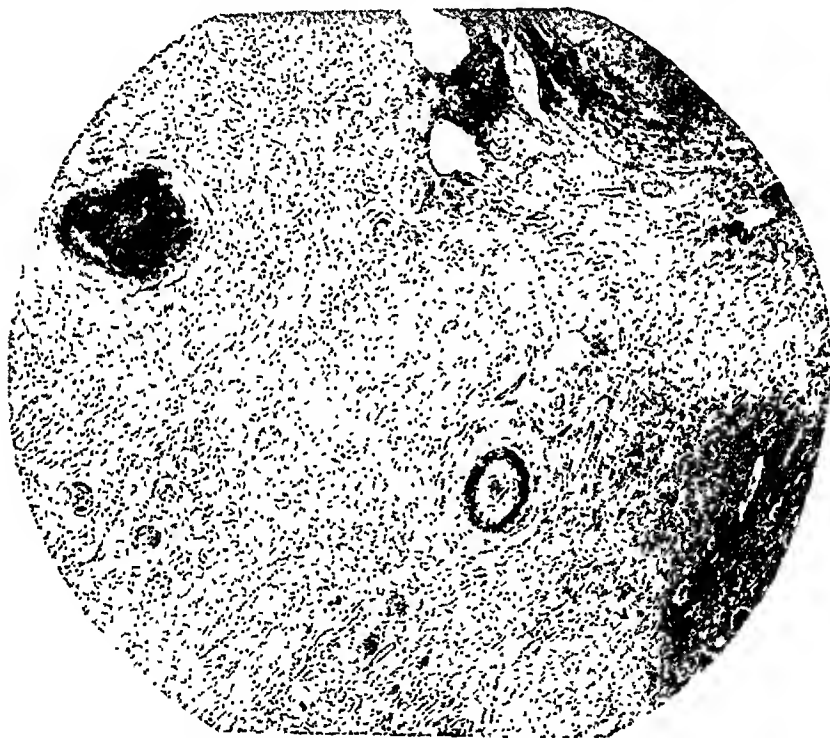


FIG. 1. Kidney showing two large vessels occluded by thrombosis and inflammatory reaction.  $\times 20$

The heart and lungs were normal on physical examination. The blood pressure was 160 mm. Hg systolic and 85 mm. diastolic. The temperature was 100° F., the pulse rate was 94 per minute, and the respirations were 22 per minute. Repeated blood studies showed a persistent moderate hypochromic anemia with a white blood cell count of 7,000 to 8,000 per cu. mm. The differential blood smear on admission disclosed 85 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, and 3 per cent eosinophiles. A blood culture and examinations of the sputum for tubercle bacilli were negative. The serum amylase was 4 units (Winslow). Repeated urinalyses were noncontributory. The epigastric pain and vomiting persisted and were associated with a continuous remittent fever to 101° and 102° F. The pain in the legs became more severe and at times skin anesthesia of both legs existed. A skin test with an antigen of *Trichinella spiralis* was negative. A diagnosis of thrombophlebitis

was made and bilateral femoral vein ligation was performed on May 13. Following the operation the pain in the legs persisted, and the patient complained of numbness of the hands and left arm. On May 21, small subcutaneous nodulations were noted along the flexor surface of the left forearm, and several days later small crusted erythematous skin lesions were seen on the arms. At this time the diagnoses of lupus erythematosus, Boeck's sarcoid, and periarteritis nodosa were entertained but lacked substantiation. Roentgenographic examinations of the chest, abdomen, and lumbosacral spine were not significant.

On May 28, an exploratory laparotomy was performed, following the sudden onset of severe right upper quadrant pain. The findings at operation consisted of focal areas of pancreatic necrosis, enlargement of periaortic lymph nodes, and a large retroperitoneal hemorrhage on the right. The hematoma extended from the duodenum to the lateral abdominal wall and from the under surface of the liver to the right iliac artery. The gall-bladder was enlarged, but contained no calculi. Cholecystectomy was performed.

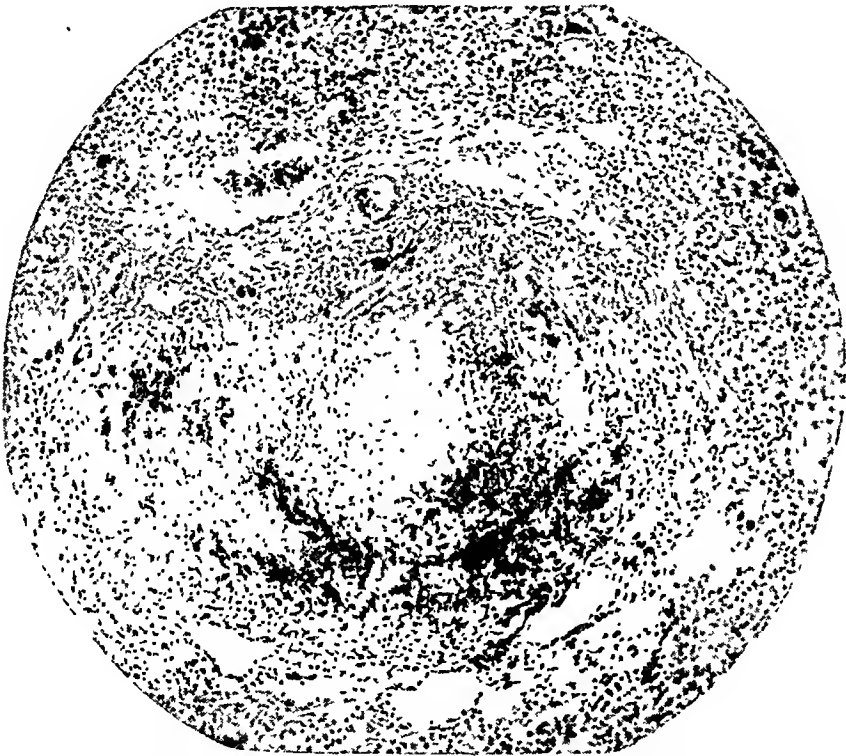


FIG. 2. Kidney showing thrombosis and necrosis of the vessel appearing to the left in figure 1.  $\times 65$ .

Following the operation the patient complained of numbness and pain in the hands and legs, had several attacks of dyspnea which were relieved by adrenalin, and vomited frequently. His condition rapidly deteriorated and he died on May 31, approximately two months following his first admission.

*Postmortem Examination.* The autopsy was performed three hours after death. There was notable pallor of the oral mucosa, and moderate abdominal distention. There was a recent right rectus surgical incision from which a small amount of bloody fluid could be expressed. Approximately 50 c.c. of clear, straw-colored fluid were present in each pleural cavity, and the upper lobe of the left lung was adherent anteriorly by numerous fibrous adhesions. The lower lobes of both lungs were mod-

erately congested. The heart was grossly normal. There was extensive atheromatous degeneration of the aortic intima, with scattered areas of ulceration. The abdominal cavity contained an estimated 75 c.c. of serous fluid. There was slight gaseous distention of the intestines. No intrinsic lesions of the gastrointestinal tract were noted.

The liver was enlarged and weighed 2,190 gm. On section the cut surface presented the typical "nutmeg" appearance of passive congestion. In the dome of the left lobe, 2 cm. beneath the capsular surface, there was a spherical hematoma which measured 1.5 cm. in diameter. Near the hepatic hilus there was a pale, softened necrotic area of infarction which measured 1 cm. in its greatest dimension. The gall-bladder contained a small amount of thick, dark green viscid bile and communicated with the surgical incision in the anterior abdominal wall. The spleen weighed 225 gm.; its parenchyma was friable, congested, and dark red in color. Numerous irregular chalky areas of fat necrosis were distributed throughout the pancreas which was bound to surrounding structures by fibrous adhesions.

Both kidneys were completely imbedded in massive, gelatinous, subcapsular blood clots. The renal capsules were intact, and had been dissected from the underlying parenchyma by hemorrhage. On the right the subcapsular hemorrhage communicated directly with a hematoma in the substance of the kidney. The cut surface of both kidneys revealed numerous hemorrhagic areas which measured from .5 to 1 cm. in diameter. The cortices were thin, and there was moderate blunting of the calyces. No communication existed between the two perirenal hematomas. No gross lesions were seen in either ureter. The bladder wall was somewhat thickened and edematous, and the prostate was nodular. The adrenal glands were situated at the superior aspect of the perirenal hematomas, and were grossly normal in appearance.

*Microscopic Examination.* Microscopic sections disclosed widespread vascular lesions of an inflammatory nature, involving the thyroid, aorta, small intestine, liver, spleen, pancreas, kidney, adrenals, and prostate. The lesions were most extensive in the liver, pancreas, kidneys, and adrenals. These organs presented an extensive, widespread, acute and chronic arteritis, in all stages of development. Frequently the arterial walls were involved in an acute necrotizing process, with a heavy infiltration of polymorphonuclear leukocytes in the adventitia. In other vessels, all layers were infiltrated with both acute and chronic inflammatory cells, including numerous eosinophiles. Other vessels were nodular, thickened and fibrous, and narrowing or complete occlusion was observed in many. In all of the organs thus affected there were large areas of infarction and of interstitial hemorrhage, with resulting destruction of the parenchyma.

#### COMMENT

In spite of the fact that various agents have at one time or another been incriminated, the cause of periarteritis nodosa is unknown. The investigations of Rich,<sup>11, 12</sup> and Rich and Gregory,<sup>13</sup> who in 1943 produced the lesion experimentally in rabbits by the injection of horse serum, constitute experimental evidence that periarteritis nodosa is a manifestation of the hypersensitive state, with the arteries reacting as the so-called "shock organ," and indicate that a wide variety of substances may play an antigenic rôle in the human.

In consideration of the allergic concept, the coexistence of bronchial asthma and periarteritis nodosa, as observed in this and other reported cases,<sup>14, 15</sup> may be more than coincidental. Whether or not a relationship exists between potential antigenic factors in the two diseases is a matter of conjecture.

The pathogenesis of the perirenal hemorrhage in this case was established by the demonstration at autopsy of a direct communication between the parenchymal and subcapsular hematomas, and by the intact renal capsules. The necrotizing

process in the renal arteries resulted in rupture of the vascular wall, dissecting interstitial hemorrhage, and ultimate perforation into the subcapsular space.

### SUMMARY

A case of periarteritis nodosa, terminating with massive bilateral perirenal hemorrhage, is presented.

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## EDITORIAL

### THE EXOERYTHROCYTIC CYCLE IN MALARIA

WHEN a susceptible subject is bitten by mosquitoes infected with malaria and containing sporozoites in their salivary glands, no symptoms appear until after an incubation period of about 10 days. With or slightly before the development of clinical symptoms, parasites first are found in the blood in demonstrable numbers. Until recently there were no direct observations of the parasites during the interval between inoculation and the appearance of parasites in the blood; and their location and activities have been a matter of speculation.

Schaudinn (1903) reported that after an infecting bite the sporozoites quite promptly penetrated into the red corpuscles, and he regarded the incubation period merely as the time required for the parasites to increase in number sufficiently to become demonstrable and excite clinical symptoms. His observation or assertion was never reliably confirmed, and there is much indirect evidence to contradict it.

It has been shown by a number of observers that if sporozoites are injected subcutaneously and the tissue at the site of injection is excised after a short interval, they can be demonstrated in this tissue, and if this is inoculated into a susceptible subject, the latter will become infected. Excision of the area, however, does not protect the first subject from infection; some sporozoites quickly escape into distant portions of the body, presumably through the blood stream. If a substantial volume of blood is withdrawn shortly (within about 20 minutes) after the inoculation or infecting bite and transfused into another subject, the latter will develop malaria. Within an hour or two at the most, however, the blood loses its infectivity and does not regain it until after an interval of usually about eight days. Even a massive inoculation of sporozoites does not materially shorten this interval.

During this period the parasites must be undergoing development and multiplication, and since they are not in the blood the process must occur in the tissues, presumably in the tissue cells. This has long been known to be the case in infections with *Haemoproteus*, an allied genus of parasites of birds.

Among the first to formulate this theory clearly and follow it up systematically were James and Tate, who in 1937 and 1938<sup>1</sup> reported a study of hens infected with *Plasmodium gallinaceum*. They described nonpigmented parasites in the endothelial cells of the capillaries, particularly in the spleen, liver, kidneys and brain. In the more advanced stages these resembled the segmenting schizonts in red cells except that they were much larger, filling and distending the endothelial cells.

<sup>1</sup> JAMES, S. P., and TATE, P.: Exoerythrocytic schizogony in *Plasmodium gallinaceum* Brumpt. 1935, *Parasitology*, 1938, xxx, 128-139.

Their publication was preceded by that of Raffaele<sup>2</sup> who described similar structures in the endothelial cells of birds infected with *Plasmodium elongatum* and *P. relictum*. The earliest observation of this exoerythrocytic stage of the parasite, however, must probably be credited to Golgi who in 1893 in a study of birds infected with *P. immaculatum* described similar structures in the leukocytes and tissue cells which he interpreted as developing parasites. He also believed that this finding explained the resistance of the infection to antimalarial drugs and the tendency to repeated relapses. This important observation was made too soon for its importance to be appreciated, and it was either discredited or forgotten for more than 40 years.

The observations of Raffaele and of James and Tate stimulated many further investigations, and the presence and development of parasites in the tissue (endothelial) cells have been amply confirmed for many species of avian malaria. As direct proof, however, that this constitutes the intermediate stage between the sporozoite and the erythrocytic stage of the parasite, the evidence is less convincing, and there are discrepancies which are still difficult to explain.

Although in the case of some species the exoerythrocytic parasites were fairly numerous and easily found, in others they were very sparse and demonstrable in only a few of the infected birds; and in still other species none could be found at all. Even in species of *Plasmodium* which yield many exoerythrocytic forms, the latter may not be demonstrable until parasites have appeared in the blood (as in *P. gallinaceum* infections in hens, James and Tate). These observers also reported that in chickens infected by inoculations of blood containing *P. gallinaceum* in the erythrocytic stage only (but no sporozoites), exoerythrocytic forms subsequently developed, although at a later period in the infection. Such observations led some investigators to conclude that the tissue phase represents an alternative cycle rather than a necessary antecedent stage of development. Many of these difficulties can be solved by the plausible assumption that parasites in the tissue phase may be quite sparse and yet suffice to establish an infection; or that their distribution in the organs affected may be spotty. Recent work on the whole tends to support this view. The extensive earlier literature has been reviewed by Huff and Coulston<sup>3</sup> and by Davey.<sup>4</sup>

Following their discovery in avian malaria, many attempts were made to demonstrate parasites in the tissue cells in the malarias of man and monkeys. Although several workers described intracellular structures which they regarded as parasites, this interpretation was not accepted by the majority of

<sup>2</sup> RAFFAELE, G.: Il doppio ciclo schizogonico di *Plasmodium elongatum*, Riv. di Malariol., 1936, xv, 309-317.

Ibid.: Presumibili forme iniziali di evoluzione di *Plasmodium relictum*, Ibid., 318-324.

<sup>3</sup> HUFF, C. G., and COULSTON, F.: The development of *Plasmodium gallinaceum* from sporozoite to erythrocytic trophozoite, Jr. Infect. Dis., 1944, lxxv, 231-249.

<sup>4</sup> DAVEY, D. G.: Concerning exoerythrocytic forms and the evidence for their existence in human malaria, Trans. Roy. Soc. Trop. Med. and Hyg., 1946, xl, 171-182.



investigators (reviewed by Angelini<sup>5</sup>). Indirect evidence supporting the hypothesis of a tissue phase in man is so strong, however, that many have expressly or tacitly assumed its existence. Particularly significant are the differences in the incubation period following inoculation of sporozoites and of blood containing the erythrocytic parasites, and in the response to anti-malarial drugs. Although the incubation period following inoculation of sporozoites is relatively fixed (eight to 10 days), regardless of the size of the inoculum, after inoculation of blood it varies with the size of the dose, and it can virtually be abolished if the latter is sufficiently massive. It is easy to eliminate the parasites in the erythrocytic phase and cure (temporarily) an acute attack of malaria by any of the usual drugs (quinine, atabrine, chloroquine, paludrine), but none of these will protect from infection under natural conditions or prevent relapses in vivax or quartan malaria. (Pamaquine and pentaquine do possess this power, particularly if quinine is also administered.<sup>6</sup>)

The failure of the earlier investigators to find the tissue phase of mammalian malaria was evidently due to their not searching assiduously in the right place, attention presumably being centered on the endothelial cells in which the avian parasites were found. It remained for Shortt and Garnham to demonstrate this phase of the parasites in the parenchymal cells of the liver, both in monkeys infected with *P. cynomolgi*<sup>7</sup> and in a human volunteer infected with *P. vivax*.<sup>8</sup> After these investigators had shown what to look for and where to find it, their observations were quickly confirmed by Hawking<sup>9</sup> and by Huff and Coulston.<sup>10</sup>

Shortt and Garnham<sup>11</sup> infected monkeys, chiefly *Macaca mulata*, by subjecting them to the bites of large numbers (over 500) of mosquitoes infected with *P. cynomolgi* and subsequently injecting the ground-up bodies of the mosquitoes into the same animal. In some cases they made repeated biopsies of the liver of the same animal; in others individual animals were sacrificed at varying intervals following inoculation, and many different organs were examined. Up to the fifth day after inoculation no parasites were found. In tissues obtained from the fifth to the tenth day, inclusive, after inoculation, nonpigmented parasites were found in the parenchymal cells of the liver

<sup>5</sup> ANGELINI, G.: Incertezza dei reperti di "forme esocitocitiche" dei plasmodi della malaria umana nel midollo osseo, Riv. Parasitol., 1947, viii, 5-18.

<sup>6</sup> Editorial: Some specific antimalarial drugs, ANN. INT. MED., 1948, xxix, 746-751.

<sup>7</sup> SHORTT, H. E., and GARNHAM, P. C. C.: Pre-erythrocytic stage in mammalian malaria parasites, Nature, 1948, clxi, 126.

<sup>8</sup> SHORTT, H. E., GARNHAM, P. C. C., COVELL, G., and SHUTE, P. G.: The pre-erythrocytic stage of human malaria, *Plasmodium vivax*, Brit. Med. Jr., 1948, i, 547.

<sup>9</sup> HAWKING, F., PERRY, W. L. M., and THURSTON, J. P.: Tissue forms of a malaria parasite, *Plasmodium cynomolgi*, Lancet, 1948, i, 783-789.

<sup>10</sup> HUFF, C. G., and COULSTON, F.: Symposium on exoerythrocytic forms of malaria parasites. II. Search for pre-erythrocytic stages of *Plasmodium vivax* and of *P. cynomolgi*, Jr. Parasitol., 1948, xxxiv, 264-274.

<sup>11</sup> SHORTT, H. E., and GARNHAM, P. C. C.: The pre-erythrocytic development of *Plasmodium cynomolgi* and *Plasmodium vivax*, Trans. Roy. Soc. Trop. Med. and Hyg., 1948, xli, 785-795.

and thus far in no other tissue. These in general resembled the mature schizonts of the erythrocytic cycle, but they were larger and contained many more merozoites. The parasite on the fifth day was described as about 10.5 micra in diameter, with about 50 chromatin masses. These enlarged progressively until on the tenth day they measured 35 to 45 micra, distending the liver cell, and contained over 1000 minute merozoites. At this stage ruptured parasites were observed, from which the merozoites penetrated into the tissues and many undoubtedly entered the blood. Some were engulfed by phagocytes which collected in the tissues following rupture of the schizont. Whether some merozoites enter and infect other liver cells is not known in the case of mammalian malaria, although there is good evidence that this occurs in some types of avian malaria. Two types, micromerozoites and macromerozoites, have been described, one infecting the circulating erythrocytes, the other the endothelial cells, thus maintaining the tissue cycle. No such differentiation of merozoites has been reported in mammalian malaria.

Shortt and Garnham observed similar parasites in the liver cells of a human volunteer seven days after a heavy inoculation with sporozoites of *P. vivax*.

There is no direct evidence as to the life cycle of the parasite between the sporozoite and the schizonts observed in the liver cells on the fifth day. Shortt and Garnham believe that each sporozoite gives rise to a single schizont, but the possibility of an intermediate generation has not been positively excluded.

Shortt and Garnham<sup>12</sup> have obtained some evidence in support of the hypothesis that the parasites causing the late relapses are derived from those in the tissue phase. In one monkey infected with *P. cynomolgi* and examined by means of a liver biopsy after a clinical remission of one month, two parasites were found in the liver cells (but only after a survey of 412 histological sections). The following day the animal suffered a clinical relapse, and organisms reappeared in the blood.

It is not known whether merozoites derived from erythrocytic schizonts can enter liver cells and thus maintain the tissue cycle in mammalian malaria. This has been demonstrated in certain of the avian malarias.

These observations also throw some light on the scope of the immunity in malaria. The human volunteer was a psychotic patient who had been given malaria for therapeutic purposes 22½ months before by inoculation of blood containing the same strain of *P. vivax*. He did not develop clinical malaria following the inoculation with sporozoites. The immunity produced by his previous malaria, therefore, sufficed to suppress the erythrocytic cycle and protect him from a clinical attack, although it did not destroy the sporozoites nor prevent the development of the parasites in the tissue phase.

<sup>12</sup> SHORTT, H. E., and GARNHAM, P. C. C.: Demonstration of a persisting exo-erythrocytic cycle in *Plasmodium cynomolgi* and its bearing on the production of relapses, Brit. Med. J., 1948, i, 1225-1228.

It should be noted that the dose of sporozoites inoculated in these experiments was colossal as compared with the number presumably introduced by the bite of one or a few infected mosquitoes under natural conditions. If a sporozoite gives rise only to a single exoerythrocytic schizont, the number of the latter would probably be so sparse in such material that a direct search would be extremely tedious at best and might well be fruitless. Inoculation experiments are not helpful for this purpose. The disease in mammals can not be conveyed by inoculations of hepatic tissue containing only exoerythrocytic parasites, although the reverse is true of avian malaria.

There seems to be no reasonable doubt as to the validity of these observations, although much remains to be learned regarding this phase of the life cycle of the malaria parasite. The scientific importance of these facts is obvious. From the practical standpoint their chief immediate importance is perhaps to give a reasonable explanation for the varying effect of specific drugs on the parasite at different stages of the infection, as well as for the late relapses. They should aid in devising logical and more effective measures of treatment.

P. W. C.

## REVIEWS

*A Course in Practical Therapeutics.* By MARTIN EMIL REHFUSS, M.D., F.A.C.P., Professor of Clinical Medicine and Sutherland M. Provost Lecturer in Therapeutics, The Jefferson Medical College, Philadelphia; Attending Physician, The Jefferson Medical College Hospital, Philadelphia; F. KENNETH ALBRECHT, M.D., formerly Clinical Director U. S. Marine Hospital, Baltimore, Md., and Co-director Division of Tuberculosis Control, Kansas State Department of Health; and ALISON HOWE-PRICE, A.B., M.D., Asst. Professor of Medicine, The Jefferson Medical College, Philadelphia; Asst. Physician to The Jefferson Medical College Hospital, Philadelphia; and a group of ten collaborating contributors. 824 pages; 22 × 29 cm. with 70 plates, 1 figure, 5 tables and 2 charts. The Williams and Wilkins Co., Baltimore, Md. 1948. Price \$15.00.

This bulky comprehensive treatise is almost encyclopedic in its scope. It encompasses material assembled in teaching therapeutics to students at the Jefferson Medical College. The material is divided into four sections. The first consists of a brief outline of general therapeutic principles in which planning, prescription writing, dietary principles, nursing problems and the contents of the physician's bag are discussed in a concise and most practical manner. Section two deals with symptomatic therapy. In this section a symptom—such as, for example, vertigo—is briefly discussed and a list of causes given, followed by treatment. Instructive plates prepared by sketching essential information in diagrammatic forms on outlines of the human body, organ or anatomical area aid materially in visualizing the material presented. The third section deals with the treatment of specific disorders and comprises the bulk of the book. Each condition or disease is briefly described and detailed therapy given. Specific instructions are given for each therapeutic step recommended. The illustrations in this section are also most instructive. Section four deals with special treatment employed in eye, ear, nose, throat, skin and other special fields and is written mainly by collaborators chosen for their skill in the special field. This material is presented in a concise, readily available manner. It should prove most helpful to the general physician.

The field of therapeutics is covered in a thorough and instructive manner. Especially valuable is the plan outline of therapy followed by the details of procedures. The choice of therapeutic agents and technics is good and where several methods of treatment are available, they are also listed. This book supplies the need which has existed for a concisely written, yet comprehensive and practical coverage of the field of therapeutics.

D. G. FRIEND

*An Elementary Atlas of Cardiography.* By H. WALLACE-JONES, M.D., M.Sc., F.R.C.P.; E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P.; and E. L. RUBIN, M.D., F.F.R., D.M.R.E. 108 pages; 14.5 × 23 cm. Williams and Wilkins Co., Baltimore. 1948. Price, \$3.00.

This little book, written by members of the staff of the Royal Liverpool United Hospital, is intended to provide the medical student with a set of representative electrocardiograms and cardiac roentgenograms, to serve as an atlas, with a minimum of descriptive text. The text is too brief to present the subject adequately for students, and the illustrations too few to be of any great use as an atlas. Precordial leads are

referred to but briefly in the text, and appear in only a few of the illustrations. The section on cardiac radiology is generally better than that on electrocardiography.

The volume seems to fall short of its goal of supplying the needs of the medical student in this specialized field.

S. S.

*Hope in Heart Disease: The Story of Louis Faugères Bishop, M.D.* By RUTH V. BENNETT. 307 pages; 15 × 21 cm. Dorrance and Company, Philadelphia. 1948. Price, \$3.00.

This is a biography of Louis Faugères Bishop, American pioneer in diseases of the heart. In the first decade of the 20th century Mackenzie had firmly established clinical cardiology in Britain, practical electrocardiography had been developed in Holland by Einthoven, and the value of roentgen-rays in cardiac diagnosis had been recognized in Germany by Groedel. In America these steps of progress were not yet appreciated. It was at this time that Bishop, in the face of criticism and in defiance of accepted standards, dared to call himself a "heart specialist." A little later (1915) he was one of the founders and original Fellows of the American College of Physicians. But his greatest achievement, his biographer states, was his success as an evangelist preaching the gospel of hope for those with heart disease.

From an intimate knowledge of Dr. Bishop's life work, the author treats her subject with great sympathy. A brief sketch of his antecedents is followed by a chronological treatment of his life—through schooldays, first struggles in practice, through the throes of establishing his specialty, to the mature physician whose doctrine changed the lives of so many cardiac sufferers. Each stage is amply illustrated with extracts from the doctor's own abundant writings. A list of Dr. Bishop's publications, seven books and nearly 200 papers, concludes the volume.

The author's style at times falls below the dignity of her subject. The lives of successful men, however, are always a profitable and stimulating study, and this biography may be enjoyed by medical men and laity alike.

H. J. L. M.

*The Ciba Collection of Medical Illustrations.* By FRANK H. METTER, M.D. 224 pages; 31.5 × 24 cm. Commissioned and published by Ciba Pharmaceutical Products Inc., Summit, New Jersey. 1948. Price, \$6.50.

This large, cloth bound collection of pathologic conditions is vividly and well illustrated, and the accompanying text is adequate to supplement the pictures. Text and pictures are divided into four main sections: I. The Lungs and Chest; II. The Gastrointestinal Tract; III. Male Reproductive Organs and Male and Female Mammary Glands; IV. Heart and Aorta. The approach is mainly anatomic, with some of the surgical and etiologic aspects presented. Anomalies such as those of mammary development and hermaphroditism are pictured and described. Each picture is a representation of the fresh cadaver rather than the preserved as is usual in many anatomic publications. Color exaggerations are well employed for accentuation. Most of the composite pictures show the gross pathology, accompanied by auxiliary color interpretations of the microscopic appearance and roentgenographic aspects of the disease. Injuries and their effect on the internal organs are considered in some detail in the text and vividly pictured in the illustrations.

The book can serve for quick reference to the surgical, pathologic, anatomic and roentgenographic aspects of disease and injury and their relation to each other. The art work as a whole is excellent.

C. D. C.

*Maternity in Great Britain: A Survey of Social and Economic Aspects of Pregnancy and Childbirth.* 252 pages; 14.5 × 22.5 cm. Oxford University Press, New York. 1948. Price, \$4.00.

This objective survey of maternal and infant welfare is based on a questionnaire inquiry of 13,687 mothers in England, Wales and Scotland who gave birth to babies during a single week in March, 1946. The remodelling of health services in Britain and the marked fall in fertility since the 1870's were the primary stimulants in this effort to obtain detailed information on the social and economic aspects of childbearing. The inquiries were carried out by health visitors in the normal course of their routine duties. The principal questions investigated were the availability of maternity services to different social classes in different parts of the country, the use made of these services, their effectiveness in educating mothers and reducing mortality and morbidity among mothers and infants, the need for domestic help during pregnancy and the puerperium, and the nature and extent of present-day expenditures on childbirth. The survey emphasizes the effect of regular antenatal supervision, begun early in pregnancy, on the incidence of prematurity and neonatal deaths and on the likelihood of establishing breast feeding. The need for more suitable clinic quarters for mothers seen on an appointment basis was quite apparent from the study. A review of the place of confinement in different areas suggests the need for a greater number of improved maternity hospitals and reveals that about 65 per cent of the home confinements in Britain are conducted by midwives. There follow interesting chapters on the relief of pain in childbirth and the value of postnatal examinations. Fifty-seven per cent of the babies had been taken to infant welfare centers before they were two months old. Again unsuitable and poorly located buildings were found in many places as in the case of the prenatal clinics. Overcrowding and staff shortages were discovered leading to hurried and inadequate consultations. Figures on the medical and non-medical costs of childbearing bring out the importance of this factor as an obstacle to childbearing which the provision of free confinement care under the National Health Service Act hopes to remove. Special aspects of the inquiry deal with the prevention of prematurity, infant feeding, working mothers, and the need for domestic help during the last weeks of pregnancy and the lying-in period. This survey is quite well done and is the first large-scale attempt to collect basic information with which to measure what maternity and child welfare services are available, how fully they are used and how far they fulfill the purposes for which they were designed.

M. A. N.

*Management in Obstetrics.* By ANDREW M. CLAYE. 186 pages; 19 × 12.5 cm. Oxford University Press, New York. 1948. Price, \$3.75.

In the preface, the author, who is Professor of Obstetrics and Gynecology in the University of Leeds, advocates, for all physicians practicing obstetrics, postgraduate training leading to the degree of D.Obst., R.C.O.G. (an examination in obstetrics devised for the general practitioner). Physicians thus qualifying would not be obstetric specialists but would have a minimum of six months postgraduate experience in obstetrics. His book, dealing only with management in obstetrics, seems to be designed to aid those seeking this training.

Many of the 36 chapters are headed with appropriate quotations from literary classics which show the author's sense of humor. Important principles are emphasized in bold-face type in the text. There are only 17 illustrations, but obviously the book was intended to be used as an adjunct to one of the standard texts. In certain chapters, some operative technic is included. Some chapters include a bibliography which, in certain instances, is not too modern.

There are certain points of difference in principles of treatment in England and in the United States as exhibited in this book. Bed rest and progesterone only are advocated in the management of habitual abortion. The author believes antenatal supervision to be secondary in importance to the management of labor. Routine pelvic examination is not considered necessary, and internal clinical pelvimetry is done only if the head does not enter the pelvis at the thirty-sixth week. "There is small place for Cesarean section in the treatment of preeclampsia." The usual position for delivery is the left lateral position. Bipolar version and bag insertion are recommended in certain cases of transverse lie. In full medical induction the author gives up to 30 units of pituitary extract if necessary. In the repair of perineal tears and episiotomy skin clips or silkworm gut are used in the skin. Lateral episiotomy is recommended. For a tonic uterus, following delivery of the placenta, which does not respond to manual massage, the author advocates injecting ergometrine directly into the uterus through the abdominal wall.

In spite of these differences, this brief, practical and conservative book is a well written treatise on obstetric management which may be read with profit by the student and physician interested in obstetrics.

J. E. S.

### BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Atlas of Peripheral Nerve Injuries.* By WILLIAM R. LYONS, Ph.D., Associate Professor of Anatomy, University of California Medical School, and BARNES WOODHALL, M.D., Professor of Neuro-surgery, Duke Medical School. 339 pages; 33 × 25 cm. 1949: W. B. Saunders Company, Philadelphia. Price, \$16.00.

*Bone Marrow Biopsy: Haematology in the Light of Sternal Puncture.* By S. J. LEITNER, M.D., Reader in Internal Medicine, University of Berne (Switzerland), etc.; English Translation Revised and Edited by C. J. C. BRITTON, M.D., Ch.B., D.P.H., Consulting Haematologist to the Prince of Wales's General Hospital, Tottenham, London, and Queen Mary's Hospital, Roehampton, etc., and E. NEUMARK, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P., Lecturer in Pathology, St. Mary's Hospital Medical School, London, etc. 433 pages; 25 × 16 cm. 1949. Grune & Stratton, Inc., New York. Price, \$8.50.

*The Ciba Collection of Medical Illustrations: A Compilation of Pathological and Anatomical Paintings.* Prepared by FRANK H. NETTER, M.D. 224 pages; 31.5 × 24 cm. 1948. Commissioned and published by Ciba Pharmaceutical Products, Inc., Summit, N. J. Price, \$6.50.

*Current Therapy, 1949: Latest Approved Methods of Treatment for the Practicing Physician.* HOWARD F. CONN, M.D., Editor; Consulting Editors, M. EDWARD DAVIS, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, WILLIAM J. KERR, PERRIN H. LONG, H. HOUSTON MERRITT, PAUL A. O'LEARY, WALTER L. PALMER, HOBART A. REIMANN, CYRUS C. STURGIS, and ROBERT H. WILLIAMS. 672 pages; 28 × 20.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$10.00.

*Hindu Medicine.* By HENRY R. ZIMMER, Ph.D., Late Visiting Lecturer in Philosophy at Columbia University, etc.; Edited with a Foreword and Preface by LUDWIG EDELSTEIN, Ph.D. 203 pages; 20.5 × 14.5 cm. 1948. The Johns Hopkins Press, Baltimore. Price, \$4.00.

*An Introduction to Cardiology.* By GEOFFREY BOURNE, M.D., F.R.C.P., Physician and Physician in Charge of the Cardiological Department, St. Bartholomew's Hospital. 264 pages; 22 × 14.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$4.50.

*Practical Aspects of Thyroid Disease.* By GEORGE CRILE, JR., M.D., F.A.C.S., Department of Surgery, Cleveland Clinic. 355 pages; 20.5 × 14 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$6.00.

*The Rh Blood Groups and Their Clinical Effects—Medical Research Council Memorandum No. 19.* By P. L. MOLLISON, A. E. MOURANT and R. R. RACE. 74 pages; 24.5 × 15.5 cm. (paper-bound). 1948—Revised and Reprinted, November, 1948. His Majesty's Stationery Office, London. Price, 1 s. 6 d. net.

*The Treatment of Pneumococcic Pneumonia in the Adult.* By MORRIS F. COLLEN, M.D., Director, Department of Medicine, Permanente Foundation Hospital, Oakland, California. 166 pages; 23.5 × 15.5 cm. 1948. Permanente Foundation, Oakland, California. Price, \$3.00.



# COLLEGE NEWS NOTES

## THE NEW YORK ANNUAL SESSION

The Thirtieth Annual Session of the American College of Physicians was conducted at the Waldorf-Astoria Hotel in New York City, March 28 to April 1, inclusive, 1949, under the Presidency of Dr. Walter W. Palmer, F.A.C.P., and the General Chairmanship of Dr. Franklin M. Hanger, F.A.C.P., both of New York City, with the very able assistance of numerous committees and local Fellows.

The program was marked by the excellence of the presentations and the wide field covered. Numerous new features were introduced into the program, such as the holding of certain clinics and pathological conferences at the Headquarters Hotel rather than requiring the physicians to travel long distances to the hospitals. This plan proved popular among the attendants and profitable to the institutions because their programs at the hotel were in every instance attended to capacity—more so than in the case of several of the clinics held in hospitals. The transport of ambulant patients to these clinics presented no undue problem and well justified the plan.

The Annual Convocation was conducted with marked dignity. Fellowships were conferred upon 255 physicians coming from various parts of North America. Master-ships, in recognition of personal character, positions of influence, or eminence in the art of practice, or for attainments in medical research, were conferred upon Dr. James J. Waring, Denver, Colo., Dr. Elliott P. Joslin, Boston, Mass., Dr. Jonathan C. Meakins, Montreal, Que., and Dr. Virgil P. Sydenstricker, Augusta, Ga. The John Phillips Memorial Medal and Award was conferred upon Dr. Edwin B. Astwood, Boston, Mass., in recognition of his accomplishments in research in the field of hyperthyroidism. The James D. Bruce Memorial Medal and Award was conferred upon Dr. Stanhope Bayne-Jones, of New York, for his accomplishments in the field of preventive medicine, and the Alfred Stengel Memorial Diploma and Award was conferred on Dr. James J. Waring, of Denver, in recognition of his great service to the College in the past, his pioneering in the art of physical diagnosis, his work as a medical educator, clinical investigator and physician. Also at the Convocation the awarding of seven Research Fellowships by the College was announced, the recipients being Dr. John C. Laidlaw (Alfred Stengel Research Fellow), Dr. Stefan S. Fajans, Dr. Horace W. Gerarde, Dr. James Metcalfe, Dr. Samuel Moore Peacock, Jr., Dr. Jack L. Strominger and Dr. Edgar Woody, Jr. The Presidential Address was delivered by Dr. Walter W. Palmer, of New York City, and the Annual Convocational Lecture was presented by Dr. Henry Allen Moe, Secretary-General of The John Simon Guggenheim Memorial Foundation, of New York.

The Annual Banquet of the College was a brilliant affair, filling the Grand Ballroom of the Waldorf-Astoria Hotel. David Lilienthal, Chairman of the Atomic Energy Commission, Washington, D. C., gave the address of the day, "The Brighter Side of the Atom."

The attendance at this Annual Session of the College far exceeded that of any previous Meeting in the history of the College, there being a gross registration of 5,627, of whom 2,486 were members of the College, 1,471 were non-member physicians, 38 were guest non-physicians, 665 were exhibitors and 967 were ladies, wives of attending physicians. The largest gross registration at any previous Meeting of the College was at the Chicago Session in 1947 when the total was 4,410, made up of 1,694 members, 1,382 guest physicians, 70 guest non-physicians, 137 medical students, 518 exhibitors and 609 ladies. Physicians were in attendance from all states of the United States, the Canal Zone, Puerto Rico, Hawaii, Argentina, Australia, Canada, Colombia, Cuba, England, Finland, Germany, India, Italy, the Netherlands and the Philippines.

It should be noted that at the New York Session medical students were not admitted because of inadequate facilities. It is regretted that many members were unable to obtain seats at several of the various functions due to the exceedingly large attendance. This has resulted in the Board of Regents and the Board of Governors instituting a plan to reduce the attendance of non-members in the future. Hereafter, non-members will have to be sponsored by members of the College in advance of the Meeting and the non-member registration fee will be increased from \$15.00 to \$25.00. The College does not wish to withhold the benefits of its Meetings to interested physicians, but necessity dictates some plan by which members of the College shall be accommodated first. Many cities are no longer able to accommodate the Annual Session of the College, and, thus, restrictive measures must be taken.

The Technical Exhibit of the 1949 Annual Session was the largest and offered the most varied interest of any to the members and guests of the College. There were some 99 firms represented, occupying 122 booths.

The Editor will begin the publication of papers from the Annual Session in the ANNALS OF INTERNAL MEDICINE with the June issue, and various presentations from the New York Session will follow each succeeding month.

*The Thirty-First Annual Session* will be held in Boston, Mass., April 17-21, 1950, with Hotel Headquarters at the Hotel Statler and the Hotel Copley Plaza, and with General Headquarters for the Meeting in the Mechanics Hall. It is confidently expected that facilities will be wholly adequate to accommodate all members of the College, both in hotel rooms and in all of the meetings. Dr. Reginald Fitz, F.A.C.P., President of the College, 319 Longwood Ave., Boston 15, Mass., will be in charge of the program of Morning Lectures and General Sessions. Dr. Chester S. Keefer, 65 E. Newton St., Boston, Mass., has been appointed by the Board of Regents as the General Chairman and will be in charge of local arrangements and the program of Panel Discussions and Clinics, as well as entertainment features.

*The Thirty-Second Annual Session* will be held at St. Louis, Mo., April 9-13, 1951.

#### ELECTIONS TO MEMBERSHIP, MARCH 27, 1949

The Board of Regents of the American College of Physicians met in New York City on March 27, 1949. The following candidates were elected as Fellows or Associates of the American College of Physicians. Those elected to Fellowship are indicated in full capital letters; those to Associateship, in capital letters and lower case.

Alfred J. Ackerman, M.C., U. S. Army  
 HORST ALBERT AGERTY, Philadelphia, Pa.  
 Edwin Carter Albright, Madison, Wis.  
 F(REDERICK) GERARD ALLISON, Winnipeg, Man., Can.  
 LEE ANDERSON, San Jose, Calif.  
 HORACE ALFRED ANDERSON, Tacoma, Wash.  
 Earl Henry Antes, Evansville, Ind.  
 DANA WINSLOW ATCHLEY, New York, N. Y.  
 Morris Axelrod, Brooklyn, N. Y.

CHARLES CABELL BAILEY, Newton, Mass.  
 Seymour Samuel Balkin, Jamaica, N. Y. (V.A.)  
 PAUL SHIRMER BARKER, Ann Arbor, Mich.  
 Benjamin Baron, New York, N. Y.  
 William Henry Bates, Cottonwood, Ariz.  
 D. R. Bedford, Topeka, Kans.

PAUL BRUCE BEESON, Atlanta, Ga.  
William Henry Beierwaltes, Ann Arbor, Mich.  
GORDON IRVING BELL, Edmonton, Alta., Can.  
WILLIAM OSLER BENENSON, Flushing, N. Y.  
ADOLPH R. BERGER, New York, N. Y.  
Morton Semur Berk, Newton Center, Mass.  
Henry Scholten Bernet, Springfield, Ill.  
MAXWELL RUFUS BERRY, Atlanta, Ga.  
Howard Richard Bierman, San Francisco, Calif.  
JOHN ALFRED BOONE, Charleston, S. C.  
SIEGBERT BORNSTEIN, Oteen, N. C. (V.A.)  
William Whelan Bourke, Knoxville, Iowa (V.A.)  
Samuel Huntington Boyer, Jr., Duluth, Minn.  
Joachim O. W. Brabander, Montreal, Que., Can.  
Vernon C. Branham, Silver Spring, Md. (V.A.)  
EARL WINFREY BRIAN, Raleigh, N. C.  
Irving Benjamin Brick, Washington, D. C.  
FRANCIS STAPLES BRIEN, London, Ont., Can.  
Henry Jerome Brock, Buffalo, N. Y.  
Stephen William Brouwer, Clifton Springs, N. Y.  
GEORGE RAYMOND BROW, Montreal, Que., Can.  
Charles Howard Brown, Cleveland, Ohio  
George Emerson Brown, Twin Falls, Idaho  
WILBERT HURST BROWN, Toronto, Ont., Can.  
JOHN SYMONDS LYON BROWNE, Montreal, Que., Can.  
JAMES STEPHEN BROWNING, Indianapolis, Ind.  
BERT MONTELL BULLINGTON, Saginaw, Mich.  
Paul Axtell Bunn, Syracuse, N. Y.  
John James Bunting, Houston, Tex.  
PAUL ARTHUR BURGESSON, Warsaw, N. Y.  
Louis Emanuel Burns, Newport, R. I.

HAYES WOODROW CALDWELL, Phoenix, Ariz.  
J(ASPER) LAMAR CALLAWAY, Durham, N. C.  
PAUL BROOMHALL CAMERON, Pryor, Okla.  
Richard Gardner Canfield, Pittsburgh, Pa.  
JESSE FLOYD CANNON, Salt Lake City, Utah  
Max Caplan, Meriden, Conn.  
Paul Simon Caplan, Pittsburgh, Pa.  
Henry Ashley Carr, New York, N. Y.  
Thomas Lyle Carr, Iowa City, Iowa  
LEON DELWIN CARSON, M.C., U. S. Navy  
Robert Johnson Catlin, St. Albans, Vt.  
ORREN DANIEL CHAPMAN, Syracuse, N. Y.  
GARNETT CHENEY, San Francisco, Calif.  
LOUIS JOSEPH CHESKIN, Newark, N. J.  
Herbert Lee Clay, Jr., Louisville, Ky.  
HENRY PLETCHER CLOSE, Coatesville, Pa. (V.A.)  
SAMUEL E. COHEN, Elmira, N. Y.  
Merchant William Colgin, Waco, Tex.  
STUART RICHARDSON COMBS, Terre Haute, Ind.  
WILLIAM V. CONN, Greensburg, Pa.  
James Frederick Conner, Rochester, N. Y.

R(EASON) LOUIS COPE, Houston, Tex.  
WALTER ALLEN CRIST, Camden, N. J.  
Gary Arnold Cronk, Syracuse, N. Y.  
ROBERT WILLIAM CURRIE, La Fayette, Ind.

Virgil Clayton Daniels, Jr., St. Petersburg, Fla.  
HAL DAVIS, Roanoke, Va.  
Richard Barre Davis, Bennington, Vt.  
William Duncan Davis, Jr., New Orleans, La.  
A(lonzo) Ray Dawson, Richmond, Va. (V.A.)  
JOHN ENGLISH DEITRICK, New York, N. Y.  
C(AMILLE) JOSEPH DeLOR, Columbus, Ohio  
John D. DePersio, Oak Ridge, Tenn.  
LEWIS DEXTER, Boston, Mass.  
Henry David Diamond, New York, N. Y.  
Morris Marcus Dick, Coral Gables, Fla. (V.A.)  
ROBERT CLARK DICKSON, Toronto, Ont., Can.  
EDMOND KING DOAK, Houston, Tex.  
Kenneth Thomas Donaldson, New York, N. Y.  
Ferdinand Donath, Cincinnati, Ohio  
Charles Kendall Donegan, St. Petersburg, Fla.  
Isadore Nathan Dubin, Memphis, Tenn.  
Wolcott Balestier Dunham, Memphis, Tenn. (V.A.)

J(OSEPH) RUSSELL ELKINTON, Philadelphia, Pa.  
GEORGE FREDERICK ELLINGER, U. S. Public Health Service  
ROBERT WILLIAM ELLIOTT, Alton, Ill.  
Edwin Curtis Evans, Atlanta, Ga.  
KENNETH AUSTIN EVELYN, Montreal, Que., Can.  
DAVID WUEST EXLEY, Miami Beach, Fla.

David Earl Fader, Augusta, Ga. (V.A.)  
Benjamin B. Faguet, San Diego, Calif.  
PAUL STRIMPLE FANCHER, M. C., U. S. Army  
Thomas Wohlsen Farmer, Dallas, Tex.  
Samuel Feinstein, Ogdensburg, N. Y.  
WILLIAM ANTHONY FEIRER, Narberth, Pa.  
GEORGE KINGSLEY FENN, Beverly, Mass.  
LUCIAN MINOR FERRIS, Vicksburg, Miss.  
HARRY THOMAS FOLEY, II, Castle Shannon, Pa.  
Paul Jones Fouts, Indianapolis, Ind.  
NATHAN FRANK, Jersey City, N. J.  
Jerome S. Frankel, Cleveland, Ohio  
Myron A. Freilich, Zanesville, Ohio  
HENRY FULLER, Lakeland, Fla.

Jacques Lester Gabrilove, New York, N. Y.  
CHARLES LEON GASS, Sackville, N. B., Can.  
WILLIAM IRVIN GEFTER, Philadelphia, Pa.  
Henry Gibbons, III, San Francisco, Calif.  
JOHN PAUL GIBSON, Abilene, Tex.  
Elmer Wilhelm Gilbert, Alhambra, Calif.  
ISADORE WILCHER GINSBURG, Philadelphia, Pa.  
ROBERT EARLE GLENDY, Roanoke, Va.

DONALD LOCKHART GLENN, Urbana, Ill.  
 RUBIN LEONARD GOLD, San Francisco, Calif.  
 WALTER GOLDFARB, New York, N. Y.  
 ALLAN MICHEL GOLDMAN, New Orleans, La.  
 PHILIP GOLDSTEIN, New York, N. Y.  
 Samuel Zangwill Goodman, Los Angeles, Calif.  
 Arthur Gordon, Woodside, L. I., N. Y.  
 Maurice Gore, Chicago, Ill.  
 Warren Frederic Gorman, New York, N. Y.  
 M(ACK) LEONARD GOTTLIEB, New York, N. Y.  
 EDWIN MATTHEW GOYETTE, M.C., U. S. Army  
 John Joseph Grady, Lakewood, Ohio  
 Irving Graef, New York, N. Y.  
 Clyde Cornelius Greene, Jr., San Francisco, Calif.  
 GEORGE SMITH GRIER, III, Newport News, Va.  
 Peter Vincent Gugliuzza, Bellerose, N. Y.  
 Edward George Gullord, Montclair, N. J.

Woodhull Stanton Hall, Bennington, Vt.  
 Morton Hamburger, Cincinnati, Ohio  
 FREDERICK CARLYLE HAMILTON, Toronto, Ont., Can.  
 Ottis Eugene Hanes, Atlanta, Ga.  
 HANCE FRANCIS HANEY, Portland, Ore.  
 Irving John Haussmann, Philippi, W. Va.  
 GEORGE THOMAS HARRELL, JR., Winston-Salem, N. C.  
 William Henry Harris, Jr., Richmond, Va.  
 Marlow Bristow Harrison, San Francisco, Calif.  
 Harold Ira Harvey, Berkeley, Calif.  
 JAMES PAISLEY HENDRIX, Durham, N. C.  
 George Carl Hennig, New York, N. Y.  
 JOHN SEVERY HIBBEN, Pasadena, Calif.  
 John Bamber Hickam, Durham, N. C.  
 Cotter Hirschberg, Denver, Colo.  
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J(OSEPH) LaMONTE ZUNDELL, M.C., U. S. Navy

#### ALABAMA MEMBERS PLANNING REGIONAL MEETING

Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, conducted a luncheon meeting of the Masters, Fellows and Associates of the American College of Physicians who were in attendance at the Alabama State Medical Association Meeting at Montgomery, Ala., on April 20, and outlined the plans for a Regional Meeting of the College to be held at Birmingham in the Autumn. The Regional Meeting will include South Carolina, Georgia, Florida, Alabama and Cuba, the Alabama members acting as hosts.

#### SPECIALTY BOARD NOTICES

The American Board of Pediatrics, Inc., John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa. Written examinations will be held under local monitors on June 24, 1949, from 2 to 4 p.m. Oral examinations will be held at Cleveland, Ohio, September 16-18, 1949; at New York, October 21-23, 1949; and at Chicago, Ill., December 9-11, 1949.

The American Board of Psychiatry and Neurology, Inc., F. J. Braceland, M.D., Secretary-Treasurer, 102-2nd Avenue, S. W., Rochester, Minn. A special examination will be held in October at a place and on a date to be announced later. Applications for examination and requests for re-examination should be sent to the Secretary-Treasurer before June 15, 1949. This examination is in addition to the regular semi-annual examinations held in May and December.

#### TRAINING SCHOOL FOR CARDIOVASCULAR INVESTIGATORS, DEPARTMENT OF PHYSIOLOGY, SCHOOL OF MEDICINE, WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO

A twelve months training course in the disciplines of cardiovascular research for a limited number of qualified individuals will be offered with the support both of the

American Heart Association and the National Heart Institute, U. S. Public Health Service. If the enrollment warrants, the course will begin July 1, 1949; otherwise Sept. 1, 1949. For details write: Dr. C. J. Wiggers, Director of the Department of Physiology, School of Medicine, Western Reserve University, Cleveland, Ohio.

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The University of California Medical School (Medical Extension) announces a postgraduate course in the medical aspects of nuclear energy, August 29 through September 3, 1949 at the Medical Center, in San Francisco. Chairman of the course is Dr. Joseph G. Hamilton, Associate Professor of Experimental Medicine and Radiology, Associate Professor of Medical Physics, and Director of the Crocker Laboratory, University of California.

Fee for this course will be announced in the detailed program which will be mailed upon request addressed to: Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

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#### UNIVERSITY OF SOUTHERN CALIFORNIA OFFERS FULL-TIME, ONE-YEAR POSTGRADUATE COURSES

Dr. Edward C. Rosenow, Jr., F.A.C.P., Director, Extension Medical Education, University of Southern California School of Medicine, has announced the following courses to be given on a full-time basis for a period of one year, the courses being approved for graduate training and board certification:

Cardiology—Dr. George C. Griffith, F.A.C.P., Director.

Internal Medicine—Dr. Paul Starr, F.A.C.P., Director.

Dermatology—Dr. Maximilian E. Obermayer, Director.

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#### MEDICAL LITERATURE SORELY NEEDED BY JAPANESE PHYSICIANS

Medical officers in the U. S. Army report a severe shortage of medical literature for the use of the Japanese profession. The war left them in poor economic circumstances, and they cannot afford subscriptions to American journals except in rare instances. No medical literature reached Japan during the war years. A large number of Japanese doctors use the Army medical literature in the local libraries and are frequently seen to copy laboriously complete articles. Many of the American medical officers have given these Japanese doctors journals, drug house literature and other material, and have loaned them their own personal medical books.

The Deputy Surgeon General of the Army is anxious to assist in any manner possible to help supply medical literature. Colonel Francis W. Pruitt, (MC), USA, 49th Medical General Hospital, APO No. 1052, c/o Postmaster, San Francisco, Calif., is acting in an advisory capacity to the Tokyo Jikei-Kai School of Medicine and offers to be an intermediary between members of the College and some of the Japanese institutions and physicians for the distribution of any medical literature which American doctors wish to mail him. Using the above address, only domestic postage will be required.

## OBITUARIES

## COLONEL ALEXANDER T. COOPER (MC), U. S. ARMY, RETIRED

Colonel Alexander Taylor Cooper (MC), U. S. Army, Retired, died on January 2 of this year in San Juan, P. R., where he had made his home since retiring from active duty in 1940. Burial was in Arlington Cemetery.

Colonel Cooper was born in Yutan, Nebr., April 8, 1883. He attended Bellevue College, Bellevue, Nebr., and was graduated from the Medico-Chirurgical College of Philadelphia in 1907. Two years later he entered the Army of the United States as a First Lieutenant in the Medical Corps. Training followed in the Army Medical School and in the Medical Field Service School at Carlisle, Pa. Colonel Cooper's special interest was tuberculosis.

While in Puerto Rico, Colonel Cooper, until his retirement, was Medical Chief of the Rodríguez General Hospital. His efforts were instrumental in securing PWA funds for the reconditioning of this hospital and its restoration to its present state as an excellent example of true Spanish architecture of colonial days. In 1940 he joined the staff of the School of Tropical Medicine, where his services as liaison officer between this institution and the U. S. Army in Puerto Rico during the trying days of World War II are still remembered. Colonel Cooper was a member of the medical staffs of the University and Presbyterian Hospitals, of San Juan.

Colonel Cooper was a diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians since 1930 and of the American Medical Association; and a member of the American Academy of Tuberculosis Physicians, Association of Military Surgeons of the United States, Association of Medical Veterans of World War I, and Puerto Rico Medical Association. He was also a member of the Society of the Sons of the American Revolution.

P. MORALES OTERO, M.D., F.A.C.P.

## DR. WILLIAM R. GALBREATH

Dr. William Robert Galbreath, an Associate of the College, died in San Antonio, Tex., on January 6, 1949, at the age of 37. Tragically, death occurred suddenly due to coronary occlusion after he had successfully combatted a tuberculous infection contracted while he was on military duty overseas.

Dr. Galbreath was born in Shreveport, La., where he spent his boyhood and received his early education. He held the B.S. degree from Centenary College, and M.S., M.B. and M.D. degrees from Louisiana State University. In 1942, he completed a three-year residency in medicine at the Charity Hospital of Louisiana, New Orleans, was elected to associateship in the College, and volunteered for service in the Army of the United States, affiliating with the 64th General Hospital Unit sponsored by the Louisiana State University School of Medicine. He served with distinction in the Mediterranean Theatre until he became ill in 1944, rising from the rank of first lieutenant to that of major.

Following separation from the Army and during the period of his convalescence, he held appointment and gave valuable service as Clinical Instructor in Medicine at Louisiana State University, and later as Associate in the Gilmer Chest Hospital of Shreveport. In 1948, his pulmonary lesion apparently cured, he was appointed Chief of the Tuberculosis Service in the Veterans Administration Hospital at Jackson, Miss., a post which he occupied at the time of his death.

Dr. Galbreath's friends and colleagues will remember him as an accomplished and talented musician, a capable and conscientious physician, a gentleman in the fullest sense of the word. May he rest in peace.

EDGAR HULL, M.D., F.A.C.P.,  
Governor for Louisiana

# ANNALS OF INTERNAL MEDICINE

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## THE NATURAL OCCURRENCE OF ANTITHYROID COMPOUNDS AS A CAUSE OF SIMPLE GOITER \*

By E. B. Astwood, M.D., F.A.C.P., *Boston, Massachusetts*

As more is learned about the thyroid gland the more plausible is the concept that goiter is a compensatory enlargement consequent to some interference with normal thyroid function. The subject of continuing debate, however, relates to the relative importance of the numerous factors which are known to be or which are suspected of being concerned in thyroid hormone synthesis. While there can be no question of the fact that iodine is an essential dietary ingredient; and, while it is well established that iodine deficiency is a cause of simple goiter, there is reason to believe that goiter is not always due to this cause alone. The observation that certain types of food may lead to goiter, coupled with the recent demonstration that virtually hundreds of pure chemical substances are highly effective goitrogens, suggests that a reëxamination of the problem might be worthwhile. If an active antithyroid agent be concerned in the occurrence of endemic or sporadic goiter in man, the most likely avenue of entry into the body is with the food, and among the foods which might contribute such a substance foods of vegetable origin appear to be the most likely. It will be our purpose here, therefore, to consider the possibility that goiter may sometimes be caused by the consumption of foods and especially of plant foods containing antithyroid compounds.

### SOME OLDER THEORIES

The idea that goiter might be caused by positive goitrogenic influences is not new; theories involving one or another substance as the etiologic agent date from the time of the earliest descriptions of goiter. So numerous and

\* John Phillips Memorial Lecture delivered at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 30, 1949.

From the Joseph H. Pratt Diagnostic Hospital and the Department of Medicine, Tufts Medical School.

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varied are these theories that their evaluation taxes one's interpretive capacity as the data on very few other subjects do. As long ago as 1867, Saint-Lager,<sup>1</sup> in reviewing the theories of goitrogenesis, listed the causes under 42 different categories, each of which was extensively documented. Some of these which are among the more pertinent to the present discussion are summarized in table 1. It is interesting to note that several inorganic

TABLE I  
Some Causes of Goiter Cited by St. Lager in 1867  
Waters Containing Excessive Quantities of:

Suspended matter	Gypsum	Organic matter
Calcium	Silica	Carbonic acid
Magnesium	Fluoride	Volcanic ash
Sulfurous substances	Barium	Coal and metal extractives

Waters Deficient in:

Oxygen	Iodine	Phosphate
Carbonic acid	Bromine	

Consumption of:

Vegetables	Pork	Alcohol
Milk	Fat foods	Certain cooking salts

substances which have received quite wide attention in the past two decades are listed; iodine deficiency and dietary factors, including the consumption of vegetables, are also included.

More modern methods of observation and the use of laboratory technics have not entirely resolved the problem. McCarrison,<sup>2</sup> in 1937, after a lifetime's study of goiter concluded that the causes of goiter could be summarized under four headings (table 2). Thus, 70 years after the time of Saint-

TABLE II  
Causes of Goiter According to McCarrison—1937

1. Faulty diet:
  - A. Excess of: fat, fatty acids, and lime
  - B. Deficiency of: iodine, vitamins A and C, protein, phosphate
  - C. Goiter-producing substances—cyanogen compounds
  - D. Lack of antigoitrogens present in green grass, alfalfa, steamed cabbage juice, sprouted legumes, and carrots
2. Chemical substances
 

Calcium, boron, silica, tellurium, organic acids, amines, cyanides, coal tar
3. Unsanitary conditions
4. Infections

Lager, positive goitrogenic influences retained a more prominent position in McCarrison's opinion than other factors such as iodine deficiency. The inclusion in this summary of certain types of food and certain chemical substances which might occur in foodstuffs attests the fact that food as a cause of goiter has continued to be investigated over the intervening years.

A careful analysis of the earlier experiments on food-goiter do not at present make it possible to decide which foods are, with certainty, goitrogenic. So many factors enter into experiments of this type that it is not surprising that conflicting views and contradictory results marked these earlier attempts to define the influence of foodstuffs on goitrogenesis. The importance of controlling the iodine intake was not recognized, nor was it realized that the health and age of the test animals and the environment could modify the result. Even today one cannot be too sure that experiments are free from fault, but it might be well to consider certain factors which aid in interpreting experiments designed to study goitrogenic influences.

### PHYSIOLOGIC FACTORS

An enlarging thyroid gland may indicate an increasing rate of hormone formation or it may indicate the reverse—a decreased rate which has evoked compensatory hypertrophy and hyperplasia. It may be only with great difficulty that these two opposite situations can be distinguished for morphologically the changes are the same. In each case the enlarging gland shows increased vascularity, the cells become larger and encroach upon the follicular lumina, and the colloid becomes so dilute that it may not stain with the usual dyes. Likewise, both the activated and the inhibited gland exhibits a loss of its store of protein-bound iodine. To distinguish between the two opposite situations, it would be necessary to use special criteria such as the rate of metabolism, the concentration of thyroxine in the blood, or tracer studies with radioiodine.

Under conditions of good health and rapid growth the thyroid tends to be relatively enlarged and activated; it is further activated in cold environments and after the administration of thyrotropin. It has been well established that thyroid atrophy and underfunction are associated with malnutrition and chronic ill health; a warm environment and the administration of various toxic substances likewise induce thyroid atrophy. If the adverse influence, whatever it may be, is severe enough, the thyroid suffers to an extent almost as extreme as that which follows hypophysectomy. Indeed, these factors which activate and depress the gland seem to do so by modifying the thyrotropic function of the pituitary gland.

It is likely that some of the studies on goiter in the past might be interpreted in terms of these modifications in the functional states of the thyroid gland. Perhaps a diet which may have been considered slightly goitrogenic may actually have been merely more nutritious than the control diet; the larger glands from the "experimental" diet may have been the normal ones and the "control" thyroids may have been atrophic. This factor may have contributed to the impression that high protein diets are goitrogenic. Certain environmental influences which have been found to increase the size of the thyroid may have a similar explanation.

Even when a highly potent goitrogen is administered, the extent of the

enlargement of the thyroid is dependent upon other factors. Undernutrition, toxic agents, and warm environments suppress the growth of the goiter. Rapid body growth, a good diet, and a cool environment are conducive to maximal rates of thyroid enlargement. An extreme example of this type of influence is to be observed when full cretinism is induced in rats by the administration of propylthiouracil from the time of birth. In the face of this extreme degree of thyroid deficiency the thyroid may hardly enlarge at all. It is as if the pituitary or the thyroid becomes unresponsive if complete athyreosis is induced at an early age. This situation seems similar to that described in endemic cretinism when goiter may sometimes be absent even though thyroid function is minimal or absent.

There are doubtless other factors which should be considered, such as, for example, the absorption and excretion of iodine and factors which might alter iodine metabolism. Recent studies of Riggs<sup>3</sup> have clearly shown that dogs excrete iodide very slowly and in this respect they differ greatly from man. Presumably the dog, in holding on to iodide so avidly, might require a correspondingly smaller iodide intake. Furthermore, the consumption of large quantities of chloride or bromide causes an increased rate of loss of iodide in the urine and consequently these and perhaps other anions could contribute to iodide deficiency by their effects upon the kidney. Thus, there might be a logical explanation for the goitrogenic influence of drinking waters which contain large amounts of various salts, and for the increased iodine requirement of animals fed on diets to which one or another electrolyte is added in excess. Unfortunately, little is known about factors which influence iodide excretion in other animals and man.

### GOITROGENIC EFFECT OF CERTAIN PLANTS

Wide interest in the possible goitrogenic influence of certain vegetable foodstuffs dates from the studies of Chesney, Clawson, and Webster.<sup>4</sup> Goiter was unexpectedly encountered in rabbits which were being maintained in the laboratory for other purposes, and these workers made detailed observations on the phenomenon. They finally concluded that the goiter was due to cabbage which formed the major part of the dietary intake.

Within a few years these findings had been confirmed from several quarters. Marine and his co-workers in New York did extensive studies on the nature of the active ingredient of cabbage and extended the field by showing that other related plants such as brussels sprouts, cauliflower, and steamed turnip root were also goitrogenic. Mangel root was found to have a slight effect.<sup>5</sup> Marine and his co-workers tackled the problem with enthusiasm; they were apparently able to reproduce the goiter with ease, and large goiters developed in incredibly short periods of time. They stated, for example, that palpable goiters would develop in 10 to 15 days when steamed cabbage was fed. By 1932, Marine, Bauman, Spence, and Cipra<sup>6</sup> concluded



that the active ingredient was an organic cyanide and that goiter could readily be induced with acetonitrile.

Many subsequent investigators have been unable to induce goiter consistently by feeding cabbage. For example, Spence, Walker, and Scowen<sup>7</sup> in continuing the study of goiter induction by cabbage and by acetonitrile encountered difficulty. Often, cabbage failed to cause any goiter at all and Spence suggested, as had Marine,<sup>8</sup> that certain foods contained antigoitrogens. He also found that small amounts of iodine would prevent goiter formation. Spence,<sup>9</sup> in 1933, made the very interesting observation that methylcyanide was less goitrogenic for chickens than for rabbits and that correspondingly chickens failed to convert the acetonitrile to thiocyanate as did rabbits. This observation appears to be the first which incriminates thiocyanate in this problem. It is unfortunate that in one experiment, presumably in four rabbits, thiocyanate had been found inactive.<sup>10</sup> Perhaps it was for this reason that the interesting thiocyanate lead was not followed up. Its goitrogenicity was not discovered until Barker's observations on man two years later.<sup>11</sup>

Meanwhile, cabbage goiter as an entity was readily confirmed by McCarrison in India.<sup>12</sup> He also found acetonitrile to be effective<sup>13</sup> and noted very striking goitrogenesis from soya beans and peanuts even when large iodine supplements were added.<sup>13,14</sup> Indeed, as an example of the difficulty one encounters in trying to interpret these findings, pigeons were observed to develop goiter as a result of iodine administration alone.<sup>13</sup>

The year 1933 marked the appearance of the first of an extensive series of studies on "cabbage goiter" from Dunedin, New Zealand. Hercus and Aitken<sup>15</sup> found that cabbage feeding sometimes gave rise to small goiters in rabbits but often no effect was observed. Far more consistent results were forthcoming when other brassica plants were employed.<sup>16</sup> Turnip roots produced goiter in two out of 14 rabbits after 60 days of feeding. Rats were soon found to be more suitable than rabbits and when they were fed brassica seed for 30 days, goiter resulted with regularity. While wheat and steamed rape seed were inactive, unheated rape seed and cabbage seed, as well as the steamed seeds of white and black mustard, were highly goitrogenic. Hercus and Purves<sup>16</sup> cited the observation of goiters weighing as much as 202 grams in lambs fed on turnip. In table 3 are listed some of the vegetable foodstuffs which have caused goiter in laboratory animals.

The discovery of the goitrogenicity of rape seed permitted careful studies on the mechanism of action. Prior to this, goiter production from cabbage and related plants was a variable and inconstant phenomenon. The incorporation of rape seed into an otherwise normal diet permitted the animals to thrive; the use of rats made it possible to observe larger numbers of animals and facilitated operative procedures. In 1941 Kennedy and Purves<sup>19</sup> and Griesbach<sup>21</sup> showed that the hyperplastic changes in the thyroid were associated with cellular changes in the pituitary similar to those which follow thyroidectomy. Furthermore, it was shown<sup>22</sup> that no goiter developed if

TABLE III

Vegetables Found to Be Goitrogenic in Laboratory Animals

Cabbage	Chesney, Clawson, and Webster <sup>4</sup>	1928
Brussels sprouts and cauliflower	Marine, Bauman, and Cipra <sup>5</sup>	1929
Kohlrabi	Stiner <sup>17</sup>	1933
Soy bean and peanut	McCarrison <sup>14</sup>	1933
Turnip and seeds of:		
mustard, rape, and cabbage	Hercus and Purves <sup>16</sup>	1936
Radish	Indina <sup>18</sup>	1940
Seeds of: rutabaga, chou moellier,		
soft and hard turnip	Kennedy and Purves <sup>19</sup>	1941
Kale, mangel, red cabbage,		
lentils, and peas	Blum <sup>20</sup>	1942

the hypophysis were removed. Later it was found <sup>23</sup> that excess iodine only partly suppressed the goiter, while thyroxine in physiological doses completely inhibited the thyroid enlargement.

These experiments clearly established that the mechanism of the goitrogenesis from rape seed is the same as that later elucidated for the sulfonamides and thioureas; that is, the primary effect is one of thyroid inhibition. The brassica seed, like the thioureas and sulfonamides, inhibits thyroid hormone synthesis. As a consequence of this, thyrotropin is secreted in larger quantities from the pituitary and compensatory hyperplasia of the suppressed thyroid is the result. This effect came to be known as antithyroid and the agents responsible, antithyroid compounds. The experiments of the New Zealand workers made it a most likely probability that the brassica seed contained an antithyroid compound and this later proved to be the case.

### GOITER FROM PURE CHEMICAL SUBSTANCES

Another major contribution to the cause of goitrogenesis was made in 1941. From two laboratories in Baltimore there appeared almost simultaneously the discovery of two chemical substances which would cause goiter in rats. Richter and Clisby <sup>24</sup> had used phenylthiourea (figure 1) for taste studies in rats and had noted that sometimes this compound caused a graying

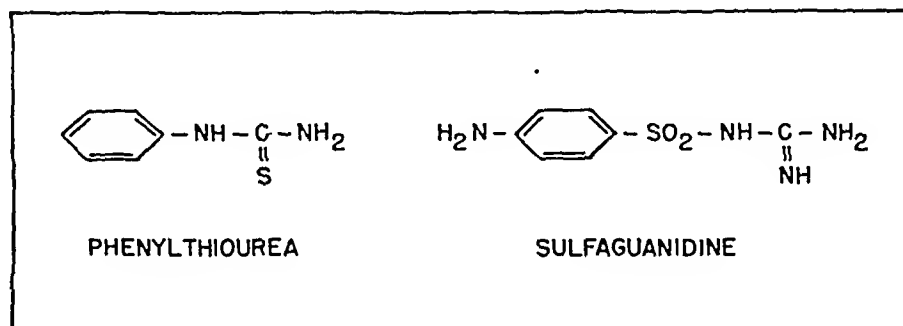


FIG. 1. The superficial structural similarity of the first two antithyroid compounds is illustrated. Phenylthiourea found to be goitrogenic by Richter and Clisby <sup>24</sup> was later shown to owe its activity to the thiocarbonamide grouping; the goitrogenic activity of sulfaguanidine discovered by MacKenzie, MacKenzie, and McCollum <sup>25</sup> proved to be a property of the aromatic amine group.

of the fur. While investigating this they made the further discovery that the compound gave rise to thyroid enlargement. MacKenzie, MacKenzie, and McCollum<sup>25</sup> were employing sulfaguanidine (figure 1) to inhibit bacterial growth in the intestinal tract for studies on nutrition. They observed that rats fed on diets containing sulfaguanidine developed marked thyroid enlargement in a short period of time. They showed clearly that the goiter could not be prevented by iodine but was completely inhibited by small amounts of thyroxine. MacKenzie and MacKenzie<sup>26</sup> then showed that other sulfonamides were goitrogenic and that thiourea itself was a highly effective goitrogen. Kennedy<sup>27</sup> in attempting to elucidate the nature of the goitrogen in rape seed considered that it might be allylthiourea and, therefore, tested this compound in rats. It, too, was found to be effective in causing thyroid enlargement.

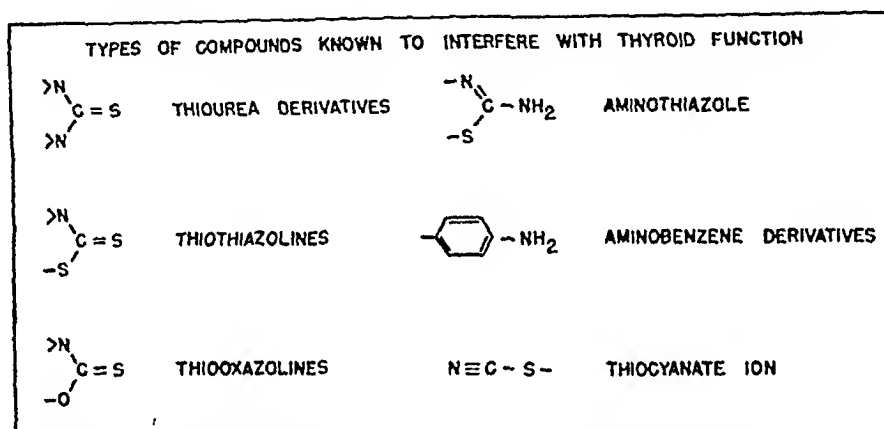


FIG. 2. The numerous chemical compounds now known to interfere with thyroid function owe their biological activity to one or another of these groupings.

Extensive studies by MacKenzie and MacKenzie<sup>28</sup> and somewhat similar ones by Astwood, Sullivan, Bissell, and Tyslowitz<sup>29</sup> led to the concept that compounds of these types inhibit thyroid hormone synthesis. The goiter develops as a secondary reaction; it represents the compensatory hyperplasia which is consequent to the hypothyroidism induced by the inhibitory agent. Further investigations into the chemical nature of the effective compounds showed that the first two compounds discovered in the Baltimore laboratories represented two distinct classes of chemical agents.<sup>30</sup> Sulfaguanidine proved to be a member of a large class of compounds which owe their goitrogenicity in rats to the presence of a free or potentially free aromatic amine group. Phenylthiourea, on the other hand, was active by virtue of the presence of a thiocarbonamide radicle; a very large group of compounds of this type proved to be goitrogenic and within this series some highly active substances were subsequently to be encountered. The several types of compound which are now known to interfere with thyroid function are shown in figure 2. MacKenzie and MacKenzie<sup>26</sup> had shown that sulfa-

guanidine was not goitrogenic in chicks; this observation, later substantiated by VanderLaan and Bissell,<sup>31</sup> further differentiated the two classes of goitrogens. The aminobenzene derivatives apparently have little or no effect in man and certain other animals, while the thiocarbonamides seem to be effective in all species of vertebrate in which they have been tested.

Meanwhile, it had been noted that though potassium thiocyanate had been found to cause goiter in man, it could not readily be caused to do so in the rat. This discrepancy was resolved when it was found that thiocyanate is only goitrogenic when the dietary iodide is low—its effect was completely abolished by adding iodide to the diet.<sup>30</sup> It is now known that thiocyanate owes its goitrogenicity to a unique effect upon the thyroid gland; it prevents the gland from concentrating iodide ion.<sup>32, 33</sup> This iodide ion-concentrating mechanism is of great importance to a normal rate of hormone synthesis when the circulating iodide is low, but when there is an abundance of iodide in the blood, enough of it enters the thyroid gland by diffusion to meet the gland's requirements.

#### COMPOUNDS KNOWN TO OCCUR IN PLANTS WHICH MIGHT BE GOITROGENIC

The extensive literature on the chemical constituents of plants is almost completely devoid of any reference to compounds of the types which are now known to be effective antithyroid agents. There are a variety of substances, however, which might properly come under suspicion, and among these are various aromatic amines, the mustard oils or organic isothiocyanates, thiocyanate ion, and the organic cyanides or nitriles.

*Aromatic amines or aminobenzene derivatives* of certain types cause goiter when administered to some animals and not others. The rat, mouse, and dog are affected by these compounds, whereas the chick and man are not influenced to a significant degree. The derivatives which are effective in the rat include numerous sulfonamides, and such compounds as diaminobenzil, diaminodiphenylmethane, various para-amino substituted aromatic sulfides and sulfones, and to a slight degree para-aminobenzoic acid. The fact that the human thyroid has not been shown to be influenced by compounds of this type makes it unlikely that aromatic amines of vegetable origin are of importance in human goiter.

*The mustard oils* or organic isothiocyanates have never been shown to exert a goitrogenic effect. They are such highly irritating substances that only minute amounts can be administered without grave effects upon the well being of the test animals. However, they are widely distributed in the vegetable kingdom and are found in especial abundance in the mustards and their close relatives where they occur in the form of glycosides from which the free isothiocyanate is liberated by enzymatic action. The reason for suspecting isothiocyanates is their close chemical relationship to agents of known effectiveness. In the presence of ammonia they readily give rise to

monosubstituted thioureas (figure 3), and the corresponding disubstituted thioureas are formed if they react with amines. It is conceivable that simple reactions such as these could take place during the process of preparing the food for eating or during mastication or digestion.

Thiocyanate ion also occurs in a great variety of plants; it has been found in considerable quantity in the mustard family but it also occurs in many other types of plant. There is said to be enough present in tobacco smoke to cause a detectable increase in the thiocyanate content of the blood, saliva, and urine of persons who use cigarettes. Large amounts are said to be found in the milk of cows fed on brassica seed and in the urine of man after eating cabbage. The known effect of thiocyanate upon the iodide ion-concentrating

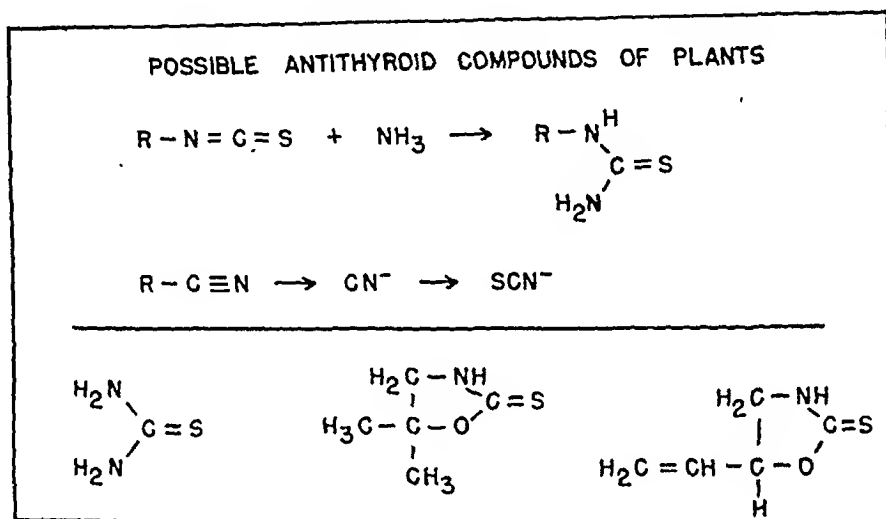


FIG. 3. Organic isothiocyanates or mustard oils readily form substituted thioureas on contact with ammonia or amines. The nitriles or organic cyanides give rise to cyanide ion in the body and this in turn is converted to thiocyanate. The three compounds in the lower part of the figure, thiourea, 5,5-dimethyl-2-thiooxazolidone, and L-5-vinyl-2-thiooxazolidone, have been detected in plants and are effective antithyroid compounds.

mechanism of the thyroid properly suggests that the consumption of foods containing this substance might contribute to the development of goiter.

There is some doubt, however, that there is a sufficient concentration of free thiocyanate in plant foods to have a significant effect. In examining this possibility, VanderLaan and VanderLaan<sup>34</sup> tested the effect of single doses of ground rape seed and cabbage seed, in quantities as large as a stomach full, on the thyroid to blood iodide ratio in the rat. No thiocyanate effect could be detected though their method could have shown the presence of as little as a tenth of a milligram. It is further possible, however, that thiocyanate may occur in plants in a combined form from which it would be liberated only after enzymatic action as in the case of the mustard oils.

The part played by thiocyanate in sporadic and endemic goiter must remain undecided at present, but its rôle as a cause of goiter is worthy of further exploration.

*Nitriles* and cyanogenetic glycosides are common and widely distributed plant constituents. As mentioned above, several nitriles have been observed to cause goiter in rabbits, <sup>6</sup> and, as already pointed out, these substances could give rise in the body to free cyanide ion which would then be converted to thiocyanate by the well-known detoxication mechanism <sup>9</sup> (figure 3). The fact that those who were successful in causing goiter in animals by the administration of these cyanides, and especially acetonitrile, also found the effect to be inhibited by added iodine would support the thought that the action on the thyroid was due to this transformation to thiocyanate. Furthermore, the influence of certain diets in increasing the blood and urine content of thiocyanate might be attributed to this conversion.

*Thioureas* were naturally suspected as possible goitrogens in food, but their rôle remains to be determined. Two plants are claimed to contain a thiourea. Thiourea itself was detected in *Laburnum anagyroides*,<sup>35</sup> and benzylthiourea has been isolated from the seeds of the tropical pawpaw (*Carica papaya*).<sup>36</sup> The possibility mentioned above of the formation of thioureas from isothiocyanates on treatment with ammonia seems not to have been entirely excluded in these two investigations. It is still uncertain, therefore, whether plants contain thiourea derivatives.

### A REINVESTIGATION OF FOOD GOITER

Investigations in our laboratory on the influence of foods were a natural outgrowth of studies on antithyroid compounds and date from 1943. After a number of compounds had been evaluated by rat tests for their possible antithyroid activity a relatively simple assay method was standardized for this purpose. <sup>37</sup> The substances were admixed with the food and administered to young rats for 10 days. Relatively large doses induced significant increases in thyroid weight while smaller quantities reduced the thyroid iodine content. This method or minor modifications of it was used in several laboratories for the evaluation of many hundreds of compounds. <sup>38, 39</sup> It seemed at that time that this technic would permit a thorough reëvaluation of the food-goiter problem, and to that end rats were fed for 10 days on a variety of vegetable foodstuffs. <sup>40</sup> The results were entirely inconclusive; no thyroid enlargement was observed, and while the iodine content of the thyroid glands was reduced somewhat the magnitude of the change was not greater than that which followed the feeding of a low iodine diet. Further progress had to await the development of better technics.

When several different compounds had been used clinically for the treatment of hyperthyroidism, it became apparent that their relative activities in man must be quite different from that which had been predicted by animal assay. For example, in France aminothiazole <sup>41</sup> was found to be highly antithyroid for man, whereas its activity in the rat had proved to be quite low <sup>30</sup>; later, propylthiouracil, which was 11 times as active as thiouracil in the rat, was found to be not nearly so active in man. These discrepancies

pointed up the need for a method of testing antithyroid compounds directly in man. Radioactive iodine made such a method possible.<sup>42</sup> The course of radioiodine collection by the thyroid gland of normal human subjects is regular and predictable; when a single dose of an antithyroid compound is given, the accumulation rate is temporarily slowed or stopped altogether. It is thus possible to compare the effectiveness of different compounds in normal people, and when this was done man was found to differ widely from the rat. For example, thiourea and propylthiouracil were approximately equal in antithyroid activity when tested in man, whereas the rat test showed propylthiouracil to be about 100 times as active as thiourea. Contrariwise, methylmercaptoimidazole was only a little more active than thiouracil in rats while it proved to be 100 times as active in man.<sup>43</sup>

It was obvious, therefore, that a food which might not be goitrogenic in rats might affect man and vice versa, and the desirability of using the human being to study the causes of human goiter was apparent. The method described above was therefore applied to foods.<sup>44</sup> A tracer dose of radioiodine was given and the rate of its collection by the thyroid was determined during the next hour or two. The subject was then enticed to eat a single item of diet in as large an amount as possible. The subsequent course of iodine accumulation in the thyroid gland showed whether or not the food contained a significant quantity of an antithyroid compound. Many foods were found to have little or no effect, some inhibited slightly, while a few were strongly inhibitory (figure 4).

From among a series of 61 different foodstuffs which had been tested in normal human subjects the yellow turnip (Swede or Rutabaga) was first selected for fractionation because of its relatively high activity and ready availability. Simple watery extracts of ground turnip contained a substance which would inhibit thyroid function in either rat or man when tested with radioiodine. After the aqueous extract was concentrated by evaporation, the active material could be extracted from the water by means of ether. Further purification led to the isolation of a pure crystalline compound which proved to be L-5-vinyl-2-thiooxazolidone<sup>45</sup>; the structure established by synthesis<sup>46</sup> is shown in figure 3. This substance proved to be about one-fifth as active as thiouracil in the rat and to have about the same activity as thiouracil in man. The quantities isolated made it highly likely that it represented the major, if not the only, antithyroid agent of turnips. It was found to be present in still higher concentrations in the seeds. This same substance was identified in the seeds of cabbage, rape, and kale, and spectroscopic evidence indicated its presence in the seeds of other brassicae, including Chinese cabbage, kohlrabi, brussel sprouts, and broccoli; it was not detected in various types of mustard seed, cauliflower seed, or in the radish, nor could it be obtained from the edible portions of cabbage, kale, broccoli, or cauliflower.

The thiooxazolidone appears to exist in the plant in a combined form from which it is liberated by enzymatic action in aqueous solution. Boiling of the uncrushed seed or root renders the material biologically inert. Aque-

ous extracts of the preheated turnip or seed contain the supposed combined form, for the compound appears upon treatment with a small amount of unheated plant tissue or upon standing in the presence of a protein fraction from the plant. The nature of the combined form or precursor has not yet been elucidated.

The possibility that a thioöxazolidone might account for the goitrogenicity of some of the brassica plants had not been previously entertained, but it is interesting to note that a related compound, 5,5-dimethyl-2-thioöxazolidone had previously been isolated from the seeds of *Conringia* or hare's ear mustard,<sup>47</sup> a plant of another genus of the Cruciferae.

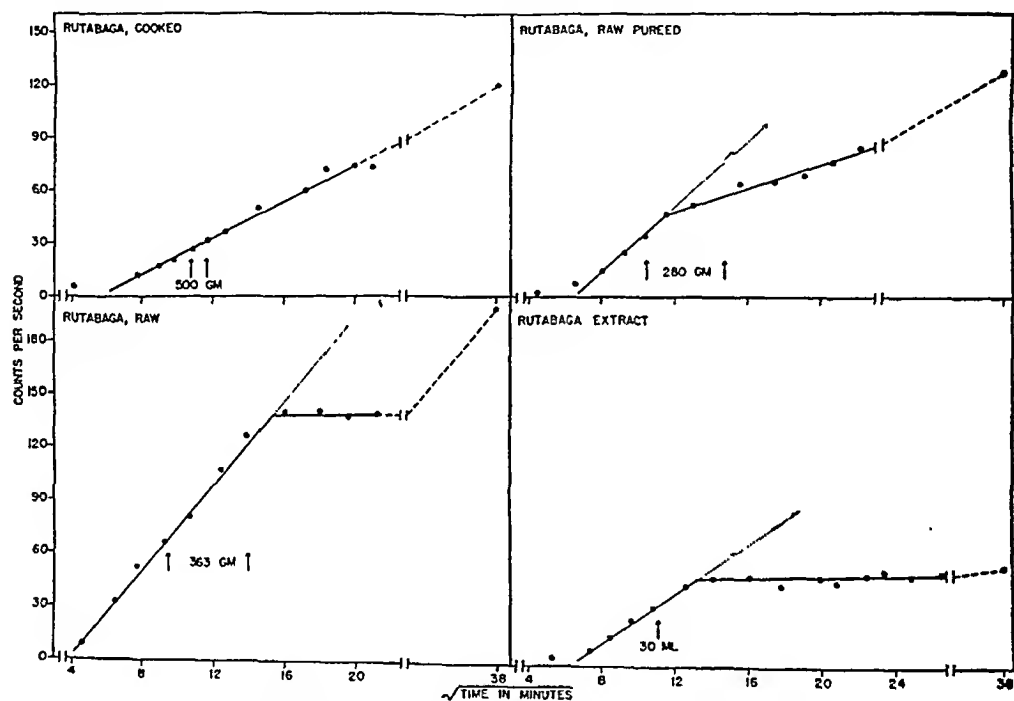


FIG. 4. Tests on cooked and raw rutabaga and on a rutabaga extract in normal human subjects using radioiodine. The cooked vegetable had no effect and the course of radioiodine collection by the thyroid gland did not deviate from the expected straight line. A moderate degree of inhibition was observed with 280 grams of raw rutabaga, 363 grams caused a complete but temporary inhibition, while 30 milliliters of extract inhibited completely for 24 hours (from Greer and Astwood<sup>44</sup>).

It would be instructive if one could reinterpret the literature on food-goiter in the light of these recent developments, but, unfortunately, there is still insufficient information to permit a full understanding. The cause of cabbage goiter remains somewhat in doubt, for while cabbage seeds contain adequate quantities of vinylthioöxazolidone to account for goiter if they are fed, cabbage leaves seem to contain too little to be detected chemically. One is left with the possibilities that cabbage goiter is due either to iodine deficiency alone, to iodine deficiency exaggerated by the presence of thiocyanate, or to iodine deficiency plus a small amount of antithyroid compound of the thioöxazolidone type. It is of course possible that some batches of cabbage



may contain this compound; if this were the case, the erratic results of cabbage feeding, cited above, might be explained.

Rape seed goiter, on the other hand, seems clearly to be attributable to the seeds' content of the newly isolated compound. This compound could also be considered responsible for the goiter of sheep fed on turnips<sup>16</sup> and for the recent epidemic of goiter in western Europe among the peoples who had to subsist largely on brassica vegetables.<sup>48</sup>

There is good evidence that mustard seeds, either heated or not, are goitrogenic in rats,<sup>16</sup> but thus far no active compound has been found in mustard. The apparent goitrogenicity of peanuts, soya bean,<sup>14</sup> radish,<sup>18</sup> carrot, and pear<sup>44</sup> cannot be attributed to the compound found in turnips; the possible presence of other antithyroid compounds in these foods deserves exploration.

### WHY IS NOT THE GOITROUS INDIVIDUAL MORE OBVIOUSLY HYPOTHYROID?

It has been argued that, if goiter is due to a compensatory attempt on the part of the gland to remedy deficient thyroid function, then hypothyroidism should more often be detectable in individuals with goiter. This line of reasoning presupposes that the enlarging thyroid fails entirely in its attempt to remedy the deficit. Actually, the efficiency of the enlarged vascular hyperplastic gland is doubtless increased many fold. This increased efficiency is readily perceived if one examines the consequences of iodine deficiency. Under normal circumstances the thyroid is presented with iodide ion in a concentration of roughly one microgram per 100 cubic centimeters of circulating plasma. The resting gland can then concentrate this ion 20- to 50-fold so that there can be available in the thyroid cell a concentration of 20 to 50 micrograms per cent of iodide, ready for synthesis into the precursors of thyroid hormone. Should there be a deficiency of dietary iodine, one might imagine that the circulating iodide might fall to very low levels, but one can calculate that a concentration of as little as one-one hundredth of a microgram per 100 cubic centimeters of plasma might still be enough to permit a normal rate of thyroid function if one considers the increased efficiency of the hyperplastic gland. It has been shown both in man<sup>49</sup> and in animals<sup>52</sup> that the iodide ion-concentrating mechanism is highly efficient in the hyperplastic gland; such a gland can maintain an iodide ion concentration some 200 to 500 times that of the circulating blood. Now, if one adds to this 10-fold increase in efficiency for collecting iodide ion the increased rate of blood flow per unit of thyroid mass and the increase in total thyroid size, it is not inconceivable that a large hyperplastic goiter may be 100 times as efficient as a normal gland in collecting iodide from the blood. It is also known that the rate of organic binding of iodine is much more rapid in a hyperplastic gland (provided, of course, that this step is not specifically inhibited by an antithyroid compound), and this accelerated utilization of iodide ion could be a further factor in increasing the efficiency of the gland. The conclusion is

inescapable that compensatory hypertrophy and hyperplasia accomplishes its purpose and makes it possible for the thyroid to function normally in the face of drastic reductions in iodine intake.

The situation obtaining when a goiter is due to the administration of an antithyroid compound is more difficult to visualize. It would seem, however, that inhibition of this type poses a much more difficult problem for the thyroid gland. The increased iodide-concentrating capacity does little good, for the inhibition is beyond this step. Probably the increased capacity to bind iodine helps some, and it is likely that the effect of a submaximal dosage of an antithyroid compound could be completely or nearly completely countered by a sufficient degree of compensatory hyperplasia. If this be true, one should expect that the prolonged ingestion of small amounts of antithyroid substances would eventuate in goiter without myxedema. It is known, however, that full doses of an antithyroid compound given continuously to a normal individual causes both myxedema and goiter, and these two phenomena may appear almost simultaneously. Under these circumstances the goiter is the consequence of a wholly futile attempt at compensation.

The importance of the compensatory increase in the capacity of hyperplastic goiters to concentrate iodide ion is well illustrated by the effect of thiocyanate ion upon it. When the iodine intake is moderately reduced, myxedema, in association with thyroid enlargement, follows the administration of thiocyanate. This suggests again that the thyroid can make up for a low level of blood iodide by means of its special iodide-concentrating mechanism, but, when this is poisoned by the thiocyanate ion, the gland can no longer compensate and myxedema results.

This line of thought leads to the conclusion that the development of a goiter is an efficient means of counterbalancing an iodine deficiency. Compensatory hyperplasia is less effective in combating iodine deficiency when thiocyanate is present, and it may fail completely to make up for the defect in hormone synthesis induced by antithyroid compounds. As a corollary of this conclusion one might reasonably suspect that, when goiter is associated with myxedema or cretinism, the goitrogenic factor is either an extreme iodine deficiency or a positive influence, such as thiocyanate or an antithyroid compound. When goiter is unassociated with signs of hypothyroidism, iodine deficiency would be the most likely cause with a mild antithyroid influence a second, less probable, possibility.

A somewhat different conclusion would be reached if one considered the effects of treatment. Iodine deficiency goiter and that due to thiocyanate are readily prevented or reversed by added iodine while the only effective remedy for goiter due to an antithyroid compound is thyroid hormone itself. Though exact clinical data on the relative effectiveness of iodine and thyroid in the treatment of goiter are not available, many observers who have used thyroid since it was first introduced for this purpose in 1894 by Reinhold have found it a more certain remedy than iodine. Several extensive clinical experiments on the prevention of endemic goiter by increasing the iodine

intake clearly establish the effectiveness of this measure; the incidence of goiter is strikingly reduced, but goiter is by no means completely abolished by this procedure. This might suggest that some other factor besides iodine deficiency is contributing to goitrogenesis. The data cited above suggest that one of these other causes is to be found in the diet.

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# CLINICAL ANGIOCARDIOGRAPHY: A CRITICAL ANALYSIS OF THE INDICATIONS AND FINDINGS \*

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ANGIOCARDIOGRAPHY is that branch of clinical radiology which deals with the roentgenographic visualization of the thoracic cardiovascular structures during their opacification by intravenously injected radiopaque substances. Although significant preliminary investigations along similar lines of approach had been made by Forssman,<sup>1</sup> Egas Moniz, Carvalho, and Lima,<sup>2</sup> Conte, and Costa,<sup>3</sup> and Castellanos, Pereiras, and Garcia,<sup>4</sup> the work of Robb and Steinberg<sup>5</sup> in 1938 first established a practical method for the contrast visualization of the right and left cardiac chambers and great blood vessels. The technic of injection is still generally employed in its original form. During the intervening 11 years, many modifications have been devised and employed to afford serial records of the cardiovascular structures during their successive opacification following the angiocardigraphic injection. Cine-roentgenography, multiple cassette changers and automatic photoroentgen methods have been employed with success.<sup>6, 7, 8</sup> Perhaps the ideal device for angiocardigraphic recording would be one which allowed the making of serial, direct, high-quality teleoroentgenograms of the chest at rapid intervals with short electrocardiographically controlled exposures. Simultaneous films in two projections would give a two dimensional study with a single injection and permit volumetric determinations of cardiac chambers and vessels. The possibilities of such apparatus are being explored at present; equipment fulfilling the above criteria is under construction.

Elaborate apparatus of this nature will find its fullest use in larger centers only, however, and will be out of the practical range of many clinicians. For the hospital roentgenologist or clinician of more modest means, the method as originally described by Robb and Steinberg will suffice to make satisfactory diagnostic films. This statement is made following an 11 year experience with the method, during which time over a thousand patients were studied without fatality. The vast majority of these examinations were conducted in the manner originally reported and all the illustrations in this study demonstrate the diagnostic adequacy of the method.

During the past 18 months, the use of Neo-Iopax, 75 per cent (sodium iodomethamate) in angiocardiology has been studied. Four hundred

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and forty-eight have been made in 305 patients. Dosage varied from 15 c.c. in infants to 45 c.c. in adults and an occasional patient received as many as three 45 c.c. injections within an hour's time. Contrast visualization afforded by this compound has been comparable to that obtained with Diodrast, 70 per cent (diiodopyridone acetic acid diethanolamine). There have been no serious reactions. The usual reaction consists of a feeling of mild heat starting in the chest and neck and spreading throughout the body, followed at about 30 to 45 seconds after the injection by a throbbing frontal headache of negligible to considerable severity. This is apparently associated with a mild elevation of blood pressure and subsides spontaneously in five to 10 minutes. Weakness, flush, pallor and thirst are often noted. During filling of the pulmonary capillary bed, a tendency to cough is occasionally observed which can usually be controlled by the patient. In six instances transient arm pain was noted. This was usually associated with stenotic lesions of the subclavian and innominate veins or the superior vena cava and is thought to represent local venous spasm. Urticaria or angioneurotic edema has not been observed and it has not been necessary to employ epinephrine. Save for chemical thrombosis of the injected vein in an estimated 30 to 40 per cent of the cases, there have been no late reactions. Neo-Iopax, 75 per cent, in our hands has proved to be a satisfactory medium for angiocardiology. The as yet unrealized ideal contrast substance for angiocardiology would produce neither reactions nor side effects and would afford greater contrast with a much smaller injected volume.

In the 11 year period following the introduction of angiocardiology, the method has proved to be of definite diagnostic value in a variety of disorders which manifest themselves in disturbed cardiovascular relationships within the thorax. In revealing the anatomy of the cardiac chambers and in delineating clearly the form of previously indistinguishable structures, angiocardiology has immeasurably added to the precision and adequacy of roentgenologic diagnosis. Although valuable physiological data have been gained through contrast cardiovascular visualization, the chief value and direction of approach of angiocardiology have been anatomical. Angiocardiology has been of particular value in the definitive diagnosis of certain abnormal states; the findings in these conditions will be briefly described.

### CONGENITAL HEART DISEASE

The combined facilities of angiocardiology and cardiac catheterization have made possible the accurate diagnosis of the vast majority of congenital cardiac anomalies during life. The development and widespread application of surgical methods for the treatment of congenital heart disease has taken the problem of diagnosis in this condition out of the hands of the academic few and placed it into the hands of the medical profession at large. Fortunately, neither angiocardiology nor cardiac catheterization is a difficult procedure to master in terms of technic and interpretation. The clinical ap-

plication of angiocardiology to the more common congenital defects will be summarized and illustrated.

*Coarctation of the Aorta* (figure 1). Angiocardiology, in adequately demonstrating the exact, measurable anatomical features of coarctation of the aorta is indispensable in the preoperative study of this condition. The most



FIG. 1. *Coarctation of the Aorta*. Male, 54. Recurrent cardiac failure for six years. Classical physical and roentgen signs of coarctation of aorta. Blood pressure in arms 170/80; in legs 110/49. Rib notching present. *Left anterior oblique angiogram*. Aorta opacified. Note coarctation 2.5 cm. distal to origin of left subclavian artery. Dilated ascending aorta is seen, as are prominent internal mammary arteries anastomosing with superior epigastric arteries.

adequate angiocardigraphic demonstration of coarctation of the aorta is obtained in the left anterior oblique projection. The ascending aorta usually is seen to be dilated and gives rise to large brachiocephalic arteries. Markedly dilated internal mammary arteries often are seen paralleling the sternum and anastomosing with the superior epigastric arteries below. The actual site of coarctation is usually seen as a narrowing slightly distal to the site of



origin of the left subclavian artery. Generally the descending aorta fills with contrast substance and is dilated for a short distance just beyond the point of narrowing. Less frequently the site of coarctation is seen to be proximal to the origin of the left subclavian artery, a condition loosely referred to as the "infantile" type of coarctation.



FIG. 2. *Patent Ductus Arteriosus*. Female, 27. Characteristic to-and-fro murmur was present. *Left anterior oblique angiogram*. Note the dilatation of the aorta just beyond the site of origin of the left subclavian artery, an inconstant sign of patent ductus arteriosus. Diagnosis confirmed at surgical obliteration.

*Patent Ductus Arteriosus* (figure 2). The diagnosis of patent ductus arteriosus is best made by physical examination and confirmed by cardiac catheterization. Angiocardiography in this condition regularly demonstrates elevation and enlargement of the left pulmonary artery, and often reveals a dilatation of the aorta at the site of origin of the ductus.<sup>9</sup> This dilatation has been observed in two cases (of mediastinal tumor) which on

subsequent thoracotomy were shown to have neither demonstrable ductus arteriosus nor ligamentum arteriosum. In addition, the dilatation has been absent in an instance of patent ductus arteriosus proved at surgical ligation, and therefore cannot be considered to represent reliable evidence for or against patent ductus arteriosus. Reopacification of the left branch of the pulmonary artery is occasionally observed in this condition, and actual opaci-

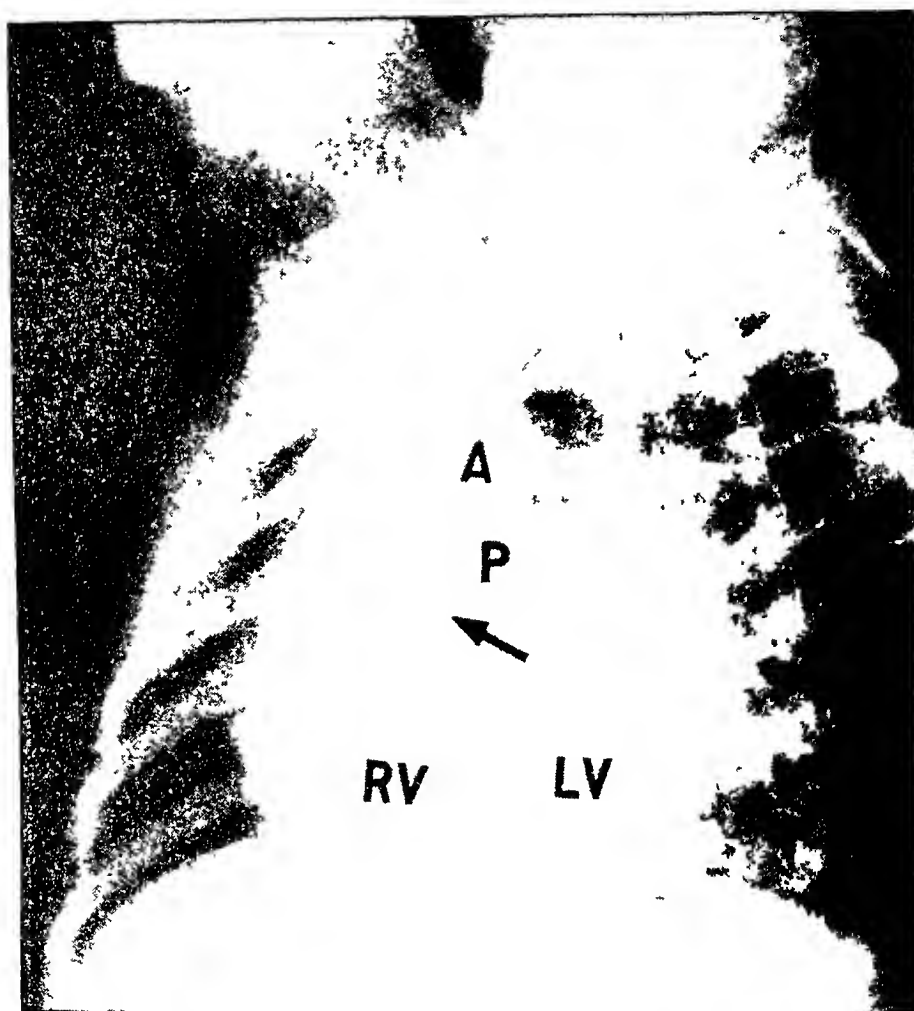


FIG. 3. *Tetralogy of Fallot*. Female, 4. Cyanosis, dyspnea since one and one-half years. Loud systolic murmur in pulmonic area. *Left anterior oblique angiogram at two seconds*. Note simultaneous opacification of aorta and pulmonary artery, stenosis of pulmonary conus and enlargement of the right ventricle. Findings confirmed at Blalock-Taussig operation.

fication of the ductus itself has been observed in two instances. Retrograde injection of the left common carotid artery with contrast substance affords far better visualization in patent ductus arteriosus than does angiocardiology although it is a more difficult and perhaps a less safe procedure.

*Tetralogy of Fallot* (figure 3). In the diagnosis of cyanotic congenital heart disease with pulmonic stenosis, angiocardiology has been of considerable value. By angiocardigraphic means, the differential diagnosis be-

tween tetralogy of Fallot and transposition of the great blood vessels, Eisenmenger's syndrome, and common truncus arteriosus may be facilitated. The surgical implications of pre-operative demonstration of the anatomy in such conditions are obvious. The various features of the usual tetralogy of Fallot are usually well seen in a left anterior oblique film made two seconds after the beginning of the injection. These signs include: (1) simultaneous opacification of the aorta and the pulmonary artery, (2) simultaneous opacification of a large right and a small left ventricle, (3) an area of stenosis in the pulmonary conus or artery and (usually) a small, poorly filled pulmonary arterial tree.

*Congenital Aneurysm of the Pulmonary Artery and Isolated Pulmonic Stenosis* (figure 4). Angiocardiography affords a method for classifying the various causes of dilatation of the pulmonary artery.<sup>11</sup> The diagnosis of congenital aneurysm of the pulmonary artery, although it cannot be made exclusively by this means, should include angiocardiographic visualization of the abnormally dilated vessel.<sup>12</sup> This is best afforded in the true lateral view which not only reveals the dilatation but also rules out the presence of pulmonic stenosis, a possible cause of pulmonary artery dilatation in the adult. In both conditions valuable diagnostic data are afforded by both the anatomic studies of angiocardiography and the dynamic information afforded by intrapulmonary artery pressure studies. The exact degree and site of isolated pulmonic stenosis as well as the often encountered post-stenotic pulmonary artery dilatation may be angiocardiographically shown and are best demonstrated in the lateral view.

*Septal Defects* (figure 5). In the interest of accurate diagnosis of congenital anomalies, it is often desirable to establish the presence and site of intracardiac shunts. The angiocardiographic diagnosis of defects in the intra-cardiac septa has been somewhat disappointing. It is regularly possible to demonstrate chamber and vascular enlargement associated with inter-atrial or inter-ventricular septal defects, but it has been possible in only a small percentage (about 30 per cent) of suspected cases to demonstrate either right to left trans-septal spread of the contrast substance or re-opacification of the right heart chambers at the time of left heart filling. A few notable and convincing exceptions to the contrary have been observed, but in general, the diagnosis of septal defect is far better made by cardiac catheterization studies. In this connection we are at present developing a method whereby we hope not only clearly to outline defects in the atrial septum, but to afford exact measurement of their size.

*Anomalous Pulmonary Veins* (figure 6). With the advent of angiocardiography the diagnosis of pulmonary veins draining into the right heart may for the first time be made during life. Although at present primarily of academic interest, this diagnosis assumes increased importance. Andrus<sup>13</sup> has suggested the possibility of surgical implantation of the anomalous vein into the left atrium. In the presence of such an anomaly, angiocardiograms

timed to show filling of the left atrium also reveal the filling of an abnormal vessel draining blood from some part of the lung and emptying into the right atrium or its tributaries.<sup>14</sup>



FIG. 4. *Isolated Pulmonic Stenosis.* Female, 23. Asymptomatic. Loud, rough, high pitched systolic murmur in pulmonic area with thrill. *Left lateral angiogram.* Arrow indicates point of stenosis in pulmonary conus below pulmonic valves. Note dilatation of mainstem pulmonary artery and branches distal to stenosis. There was no evidence of associated congenital defects.

### ACQUIRED HEART DISEASE

Many diagnostic problems related to acquired heart disease have benefited by angiocardiographic study, notably the diagnosis of syphilitic aortitis, the differentiation of aneurysm from mediastinal tumor and the diagnosis of pericardial effusion.

*Hypertension* (figure 7). Angiocardiography permits complete visualization of the unfolded aorta but otherwise adds little information to that

afforded by conventional clinical and roentgenologic methods in the diagnosis of uncomplicated hypertension. The angiocardigraphic findings in hypertension consist of the demonstration of left ventricular chamber enlargement, dilatation of the ascending aorta and unfolding of the aortic arch. These changes are best seen in the left anterior oblique view. The aorta in hyper-

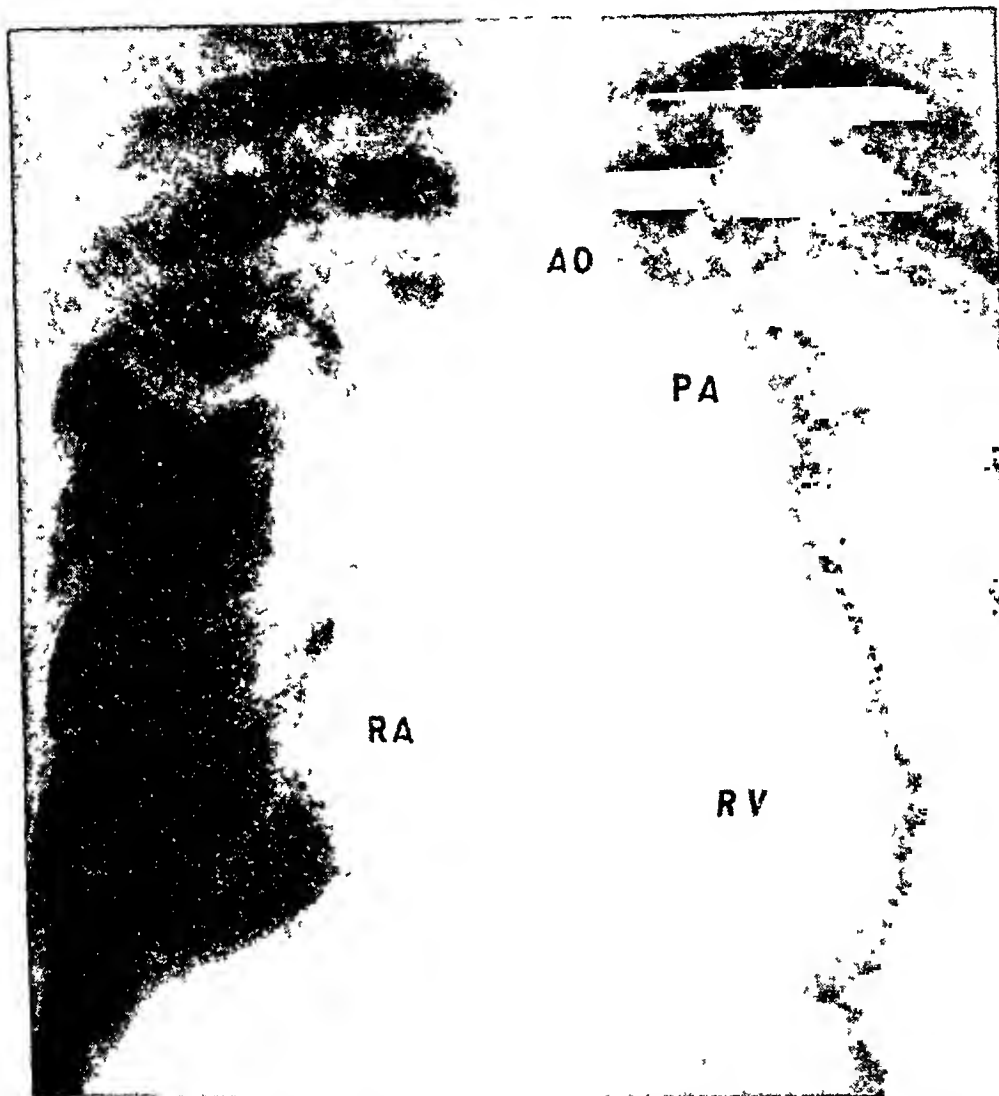


FIG. 5. *Interatrial Septal Defect.* Male, 42. Diminished cardiac reserve, 12 years. Loud systolic murmur along left sternal border and "hilar dance" on roentgenoscopy. *Frontal angiogram at eight seconds.* Note opacification of small aorta (AO), reopacification of right atrium (RA), right ventricle (RV) and tremendously dilated pulmonary artery and branches. Diagnosis confirmed by cardiac catheterization (superior vena caval blood: 7.6 vol. per cent oxygen, right atrial blood 15.4 vol. per cent oxygen).

tension may vary in size between the normal mid-ascending caliber (average, 28 mm.; upper limit, 38 mm.) to moderate dilatation (up to 46 mm. in our series). In contrast to the changes in syphilis, the dilatation is even and the lumen is customarily smooth in contour. The aortic wall is normal in thickness (2 to 3 mm.). There has as yet appeared to be no fixed correla-

tion between the duration and degree of hypertension and the amount of aortic dilatation.

*Arteriosclerotic Heart Disease* (figure 8). Aside from demonstrating the distorted course of the elongated aorta in the presence of arteriosclerotic changes and thereby differentiating it from aneurysm or tumor, angiocardiology has been of little value in arteriosclerotic heart disease. It is occa-

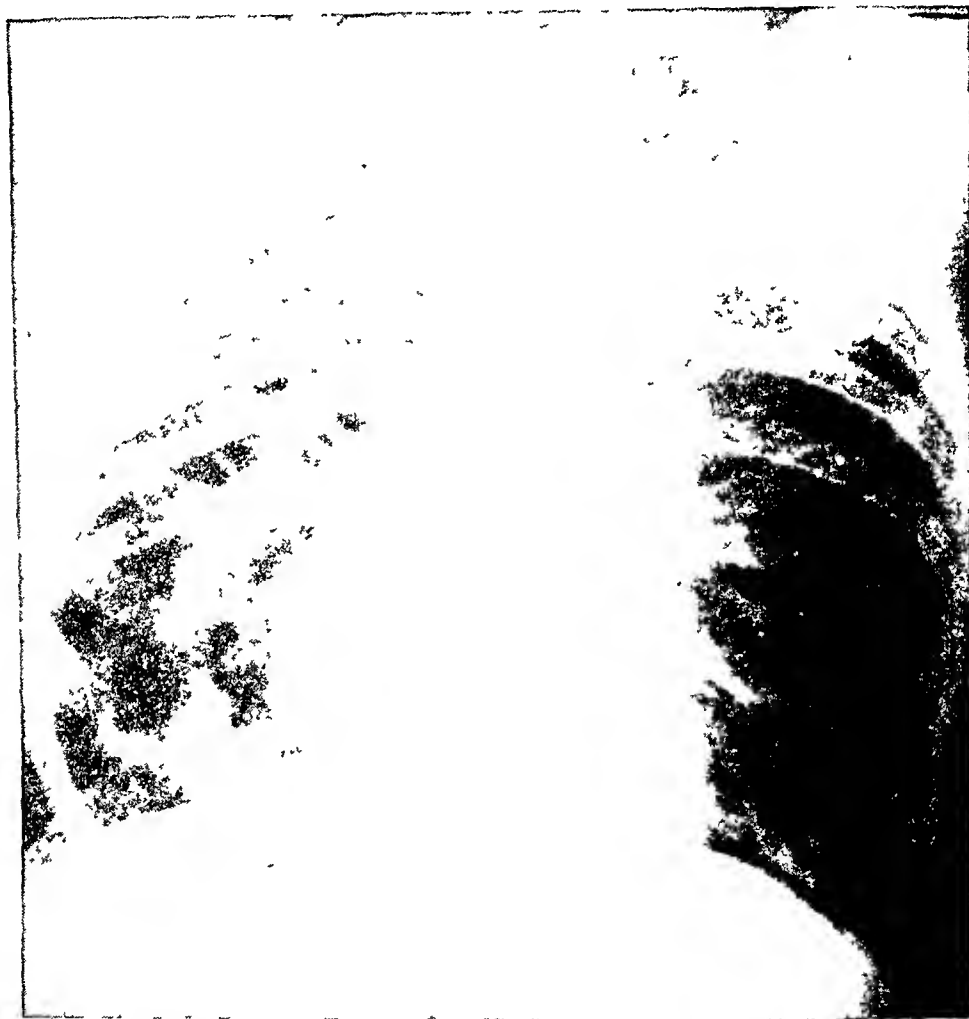


FIG. 6. *Anomalous Pulmonary Vein Entering Inferior Vena Cava.* Male, 27. Asymptomatic. Crescent-like shadow, right lower lung field found on routine chest roentgenogram. Frontal angiogram at 8.5 seconds. Note filling of left heart, pulmonary veins and aorta and simultaneous opacification of a vascular trunk draining blood from the right lung to a point below the diaphragm.

sionally difficult to distinguish between arteriosclerotic aortic elongation of the aorta and tumor or aneurysm, a distinction made with ease by angiocardigraphic means.<sup>15</sup> Arteriosclerotic plaques may rarely be visualized as localized areas of thickening of the aortic wall. Because of the increased denseness of the aortic wall in arteriosclerosis, angiocardigrams of the atherosclerotic aorta frequently show strikingly sharp contrast.

*Rheumatic Heart Disease* (figure 9). Aside from its academic interest,

angiocardiology is of little value in rheumatic heart disease wherein physical examination and conventional roentgenography are generally diagnostically sufficient. Exceptions to this lie in the differential diagnosis between marked cardiac enlargement and pericardial effusion and in the occasional demonstration of thrombi within the cardiac chambers in the presence of auricular fibrillation. Angiocardiological study of the heart has excluded

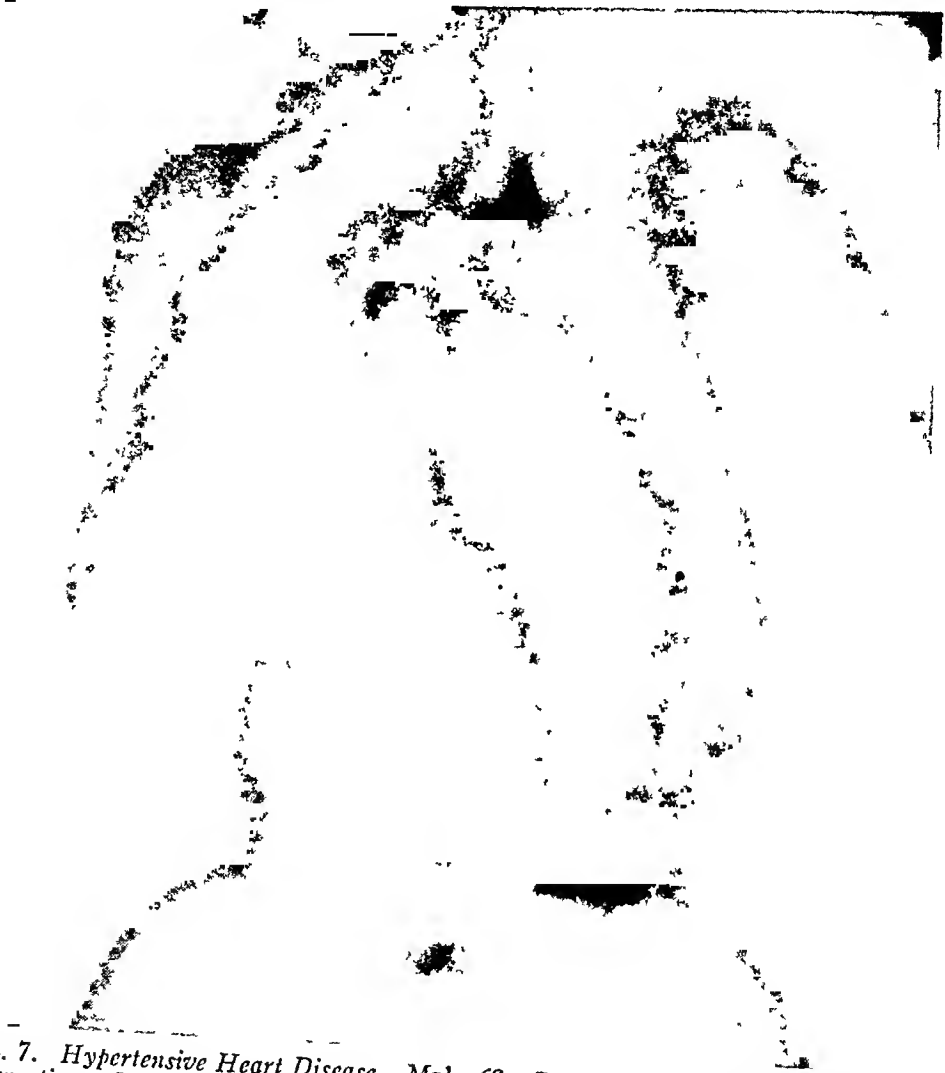


FIG. 7. *Hypertensive Heart Disease. Male, 68. Blood pressure 180/110. No apparent decompensation. Left anterior oblique angiogram. Left ventricle enlarged. Note elongated, moderately dilated thoracic aorta.*

the term "pulmonary conus" from an accurate description of the frontal roentgenogram in mitral stenosis. The prominence in the left mid-cardiac border in this condition has been repeatedly shown to consist of (1) an enlarged, elongated main-stem pulmonary artery and its left branch and (2) the left auricular appendage. The earliest angiographically observed change in mitral stenosis has consisted of enlargement of the left atrium. This is well demonstrated in the left anterior oblique view, timed to show

filling of the right heart, and with the esophagus outlined by barium swallow. The posterior deviation of the esophagus and the anterior impression on the right atrium thus outline in negative relief the enlarged left atrium. This can be borne out in films made to show left atrial filling.

*Pericardial Effusion* (figure 10). The diagnosis of fluid within the pericardial space occasionally presents considerable clinical difficulty but is made with ease and certainty by angiocardiology. Films timed to show right



FIG 8 *Arteriosclerosis of Aorta.* Male, 69. Previous myocardial infarction. Peripheral arteries markedly sclerotic. *Left anterior oblique angiogram.* Note sharply opacified, markedly elongated, tortuous thoracic aorta.

atrial opacification demonstrate the presence of an increased non-opacified area between the right atrium and the right lung field. Normally this distance represents the thickness of the wall of the right atrium and measures (as seen angiographically) not above 2 to 4 mm. Visualization of the left ventricular cavity in the presence of pericardial effusion shows its outer border to be well within the left margin of the cardiac shadow, thereby demonstrating the presence of fluid on the left side. Angiocardiology affords



virtually as conclusive proof of the existence of pericardial effusion as does pericardial tap, is more easily performed and is probably much safer.<sup>16</sup>

*Syphilitic Aortitis and Aneurysm* (figure 11). The angiocardio-graphic diagnosis of uncomplicated syphilitic aortitis represents a definite contribution toward the early detection of cardiovascular syphilis.<sup>17, 18</sup> The angiocardio-graphic signs of syphilitic aortitis are abnormal dilatation of the as-

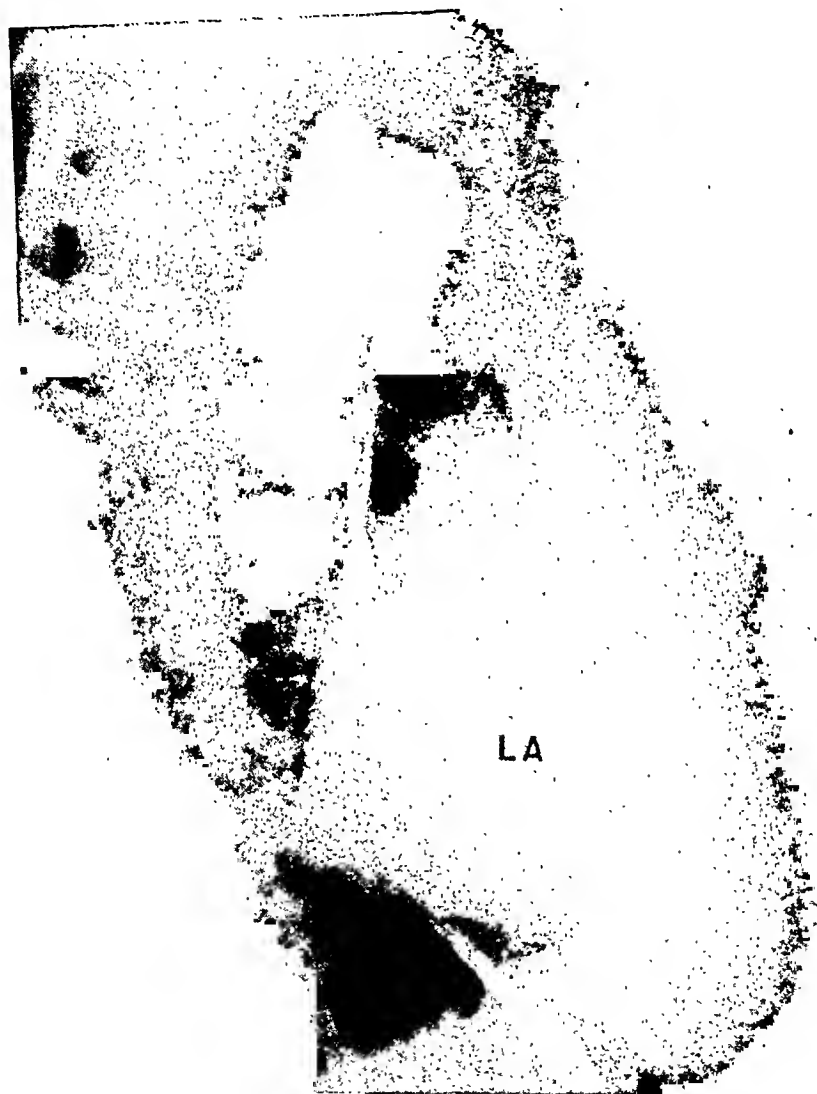


FIG. 9. *Rheumatic Mitral Stenosis*. Male, 49. Rheumatic mitral stenosis for seven years with recent cardiac failure. Typical diastolic rumble was present. *Right anterior oblique angiogram at 16 seconds*. Note opacified, markedly dilated left atrium displacing barium filled esophagus posteriorly.

ending aorta (above 38 mm., caliber), as measured in the left anterior oblique projection; irregularity of the aortic lumen; variations in aortic wall thickness, and aortic aneurysm. Dilatation, the most significant evidence of the early changes in syphilitic aortitis, must be evaluated with care since it may also be caused by hypertension, non-syphilitic aortic insufficiency, and by congenital anomalies of the aortic arch. In our experience, arterioscler-

otic changes alone rarely if ever produce significant dilatation of the ascending aorta. In this connection, the standards for aortic measurement were established by the study of films made at a six-foot tube-screen distance; figures derived from angiocardiograms made at less than that distance will be falsely higher and therefore not comparable.<sup>19</sup>



FIG. 10. *Pericardial Effusion.* Female, 56. Dyspnea three years. Large heart without physical or electrocardiographic evidence of pericardial fluid. *Frontal angiocardigram.* The wide interval between the opacified right atrium and the right heart border made possible the angiocardigraphic diagnosis of pericardial effusion. Diagnosis confirmed by pericardial tap when 400 c.c. of fluid were removed. Etiology of the effusion was never established.

The diagnosis and delineation of aortic aneurysm has been made a simple process by angiocardiology. Previously inaccessible sites of aortic dilatation such as the sinuses of Valsalva may now be clearly outlined. The rare instances of clotted aneurysms which do not fill with contrast substance are usually recognized by the demonstration of collateral evidences of syphilitic aortic disease. Angiocardiology cannot be relied upon to distinguish between syphilitic and congenital aneurysms of the aortic arch and clinical judgment must be the eventual deciding factor when this possibility arises.<sup>20</sup>

*Dissecting Aneurysm.* The changes of dissecting aneurysm of the aorta as seen angiographically are distinctive. The aortic lumen is seen to be more or less abruptly narrowed and the aortic walls thickened at the site of the dissection. Contrast substance has been angiographically demonstrated within false passageways formed by dissecting aneurysms.<sup>21</sup>



FIG. 11. *Syphilitic Aortitis.* Male, 56. Late, untreated syphilis. Blood pressure 135/75. Clinical diagnosis of possible syphilitic aortitis based upon aortic systolic murmur. *Left anterior oblique angiogram.* Note opacification of irregularly dilated ascending aorta which measured 42 mm. in caliber.

*Pulmonary Heart Disease* (figure 12). Although the diagnosis of pulmonary heart disease is best arrived at by studies of cardiac and pulmonary function, early morphologic changes may frequently be demonstrated by angiography. Left anterior oblique angiograms reveal enlargement of the right ventricle, while lateral and frontal films reveal enlargement of the pulmonary artery and its branches. Elongation, followed by dilata-

tion of the pulmonary artery are early changes in pulmonary heart disease. These probably occur concomitantly with right ventricular hypertrophy and elongation of the pulmonary conus. In all probability the earliest demonstrable abnormalities in pulmonary heart disease are physiological rather than anatomical, as far as the cardiovascular system is concerned.<sup>11</sup>



FIG. 12. *Cor Pulmonale*. Male, 71. Dyspnea, cough for many years. Physical and roentgen examination revealed marked pulmonary emphysema. *Left lateral angiogram*. Note opacification of markedly enlarged right atrium, right ventricle (RV), pulmonary artery (PA) and its branches. Right pulmonary artery (RPA) is seen end-on. Arrow indicates interventricular septum.

*Constrictive Pericarditis* (figure 13). The operative relief afforded patients with constrictive pericarditis has long been recognized, and complete study in this condition is therefore of more than academic value. Although angiocardiography is unnecessary in making the diagnosis,<sup>22</sup> it adds otherwise unobtainable information to the study of individual cases. The angiographic findings in constrictive pericarditis vary among cases, but usu-

ally include the demonstration of a grossly dilated superior vena cava merging imperceptibly into a dilated right atrium. The ventricular cavities are usually found to be normal or reduced in size, as would be anticipated. The thickness of the ventricular wall plus the thickened pericardium may often be demonstrated, and contrast studies aid in the localization of pericardial or myocardial calcifications.



FIG. 13. *Constrictive Pericarditis.* Male, 49. Ascites, dependent edema and dyspnea, two years. Markedly elevated venous pressure, paradoxical pulse. Calcification of pericardium seen on conventional roentgenogram. *Left anterior oblique angiogram at two seconds.* Note opacification of dilated superior vena cava and right atrium. The right ventricular wall appears thick and contains or is surrounded by calcification.

### MEDIASTINAL TUMORS

Contrast visualization of the cardiovascular structures in the pre-operative investigation of mediastinal tumors affords otherwise unobtainable diagnostic and prognostic information. Angiocardiography, by outlining cardiovascular structures in contact with the inner or "hidden" margins of

mediastinal tumors, serves to delimit and more accurately localize the mass within the mediastinum as well as rule out the presence of aneurysm. Further evidence of a differential nature is gained by the demonstration of the effect of a tumor upon the thoracic great blood vessels. Thus, while a dermoid cyst may be seen to displace major vessels, a malignant thymoma



FIG. 14. *Malignant Mediastinal Tumor.* Female, 38. Edema and cyanosis of face, neck, arms and chest for four months. Venous pressure in arms 300. *Frontal angiocardio-gram at two seconds.* Note multiple filling defects of superior vena cava and extensive venous collateral channels. Biopsy of anterior chest wall lesion one year later showed carcinoma, primary site unknown.

or teratoma shows a tendency to cause stenotic or obstructive changes. By demonstrating to the surgeon the structures bounding a mass to be extirpated, angiocardio-graphy aids in planning operative attack.<sup>23</sup>

*Benign Mediastinal Tumors.* Bronchiogenic, dermoid or pericardial cysts are usually demonstrable angiocardio-graphically as single masses causing a variable degree of displacement of the great blood vessels or cardiac

chambers, but not producing significant obstruction to vessels. The study of such tumors should include two injections in positions at right angles to each other so as to give maximum three dimensional information of use in formulating surgical measures.

*Malignant Mediastinal Tumors* (figure 14). Contrast studies in the presence of lymphomata of the mediastinum are chiefly of value in two ways: (1) multiplicity of lesions, a diagnostic feature, may be demonstrated, (2) vascular involvement such as superior vena caval obstruction, may be shown. These features may aid in arriving at a decision as to the choice between radiation therapy and surgical approach. The angiocardio-graphic positions employed to study these as any tumors of the chest must be selected upon the basis of the location, size and shape of the mass or masses in question, and by the clinical findings. Thus in a patient suspected of having a right innominate vein obstruction, the position of choice would be the frontal position and the injection would be made in the right arm. Other malignant mediastinal tumors, both primary and metastatic, manifest equally a tendency toward stenosis and obstruction of great blood vessels.

#### BRONCHOGENIC CARCINOMA (FIGURE 15)

The angiocardio-graphic findings in bronchogenic carcinoma are those of malignant tumors in general, often have both diagnostic and prognostic application and aid in formulating surgical measures. Stenosis and occlusion of major pulmonary arteries at or near the hilar areas constitute evidence in favor of a malignant neoplastic process, although it must be borne in mind that non-malignant tumors or infectious and granulomatous hilar lymph node enlargement may by external pressure cause changes in the caliber and configuration of pulmonary vessels. As in barium study of the gastrointestinal tract, however, the distinction between extrinsic pressure defects and the changes produced by neoplastic infiltration may usually be recognized. It is frequently possible, by virtue of the demonstration of malignant involvement of central vascular structures, to arrive at an operative prognosis in a given instance of lung cancer. Sufficient experience has not been accumulated to deny the patient with bronchogenic carcinoma the possible aid of surgical intervention on the basis of angiocardio-graphic evidence of inoperability. The projection of choice for the angiocardio-graphic study of lung cancer is the frontal projection since this affords the best view of the pulmonary vessels and of the hilar and mediastinal structures.

#### CHRONIC PULMONARY DISEASE

Both anatomical and dynamic changes in the vascular supply to affected portions of the lungs may be shown by contrast visualization in the presence of various chronic pulmonary disorders. In tuberculosis a relative hypovascularity is seen, and in the presence of long-standing disease, there is seen distortion and displacement of the pulmonary vessels which is incident upon fibrosis and cicatricial changes. Bronchiectasis is often associated with ap-

parent poor filling of the pulmonary arteries supplying the affected lobes, while in pulmonary emphysema, and particularly the localized bullous type, the separation of pulmonary artery radicles by emphysematous areas of lung parenchyma is often striking. In the presence of atelectasis, filling of the vessels to the collapsed area of lung is poor, and these vessels are seen to be

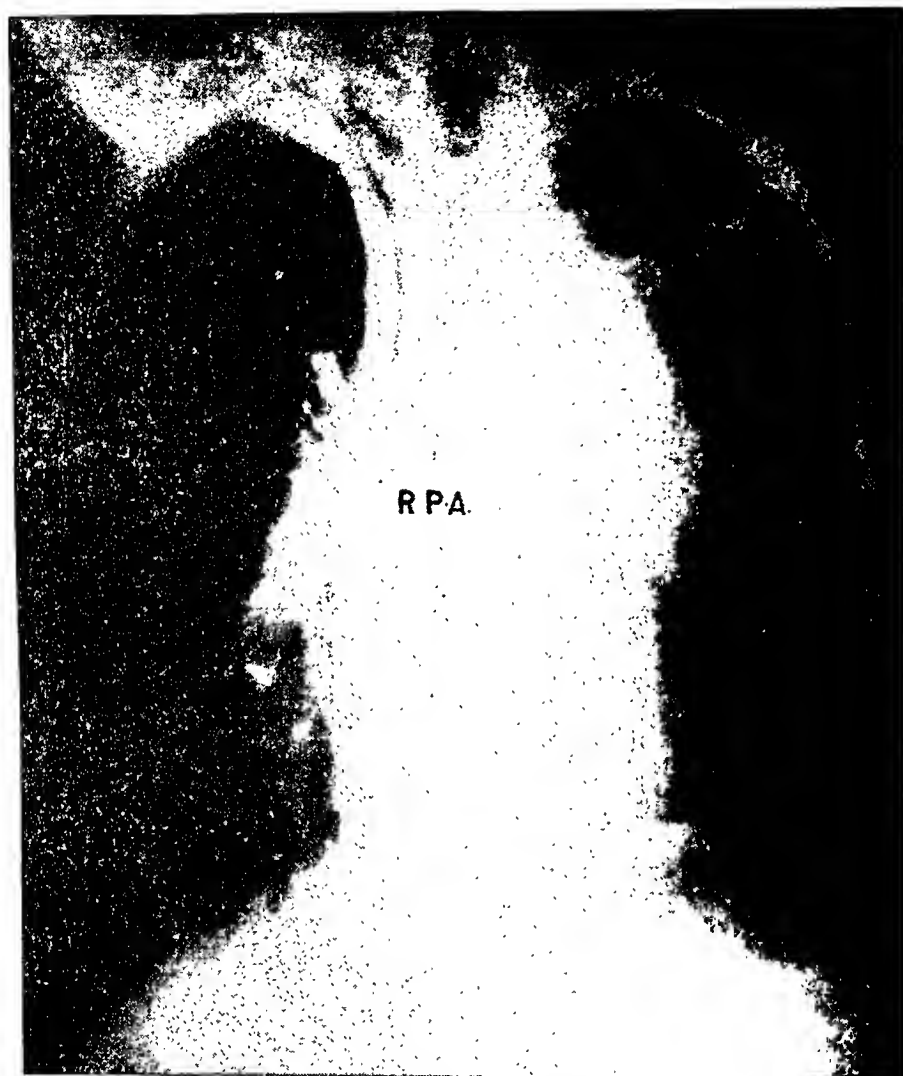


FIG. 15. *Bronchogenic Carcinoma*. Male, 51. Weight loss, cough, dyspnea and left chest pain for a year. *Frontal angiocardigram*. Note complete occlusion of left pulmonary artery by tumor in left upper lung field. The opacified right pulmonary artery (RPA) is dilated. Exploratory operation confirmed the findings.

crowded closely together, findings which aid in the more accurate identification and localization of areas of atelectasis.<sup>24</sup> Diminished vascularity is seen in the presence of pneumothorax.<sup>25</sup>

#### THORACIC DEFORMITY (FIGURE 16)

The displacement of heart and great blood vessels in kyphoscoliosis, thoracoplasty, pneumothorax, and following pneumonectomy and lobectomy



may be delineated with ease angiocardigraphically, and certain physiological data may be obtained concerning cardiopulmonary function in such instances. Following pneumonectomy, or in the presence of a non-functioning lung, the increased circulation to the remaining or functioning lung is often indicated by the demonstration of an enlarged branch of the pulmonary artery supplying that side.

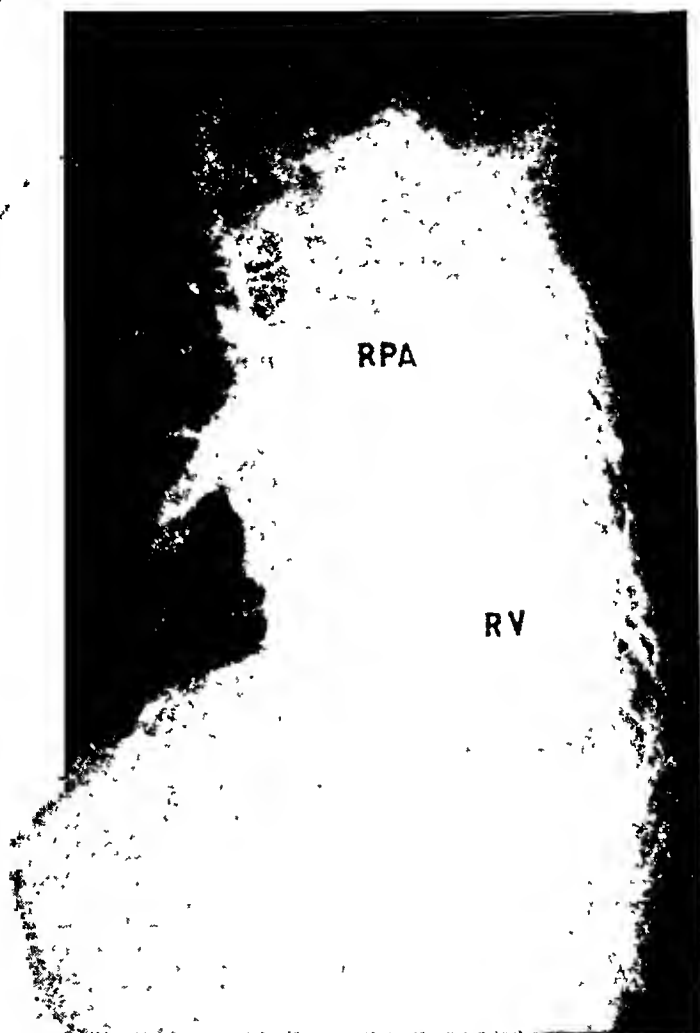


FIG. 16. *Pneumonectomy. Female, 10. Pneumonectomy for extensive left lung bronchiectasis three years previously. Frontal angiogram. Note pronounced rotation of heart and blood vessels into left chest. The right pulmonary artery is considerably enlarged.*

### SUMMARY AND CONCLUSIONS

During the past 11 years, the angiocardigraphic study of over 1,000 patients has been conducted without fatality, thus indicating the safety of this diagnostic method. In the presence of certain pathological states, angiocardigraphy has emerged as an indispensable diagnostic technic. Contrast cardiovascular visualization has been shown to be of its greatest value in the diagnosis of the following conditions: Coarctation of the aorta; tetralogy of

Fallot and related lesions; isolated pulmonic stenosis; anomalous pulmonary veins; aneurysms, congenital and acquired; pericardial effusion; uncomplicated syphilitic aortitis; mediastinal tumors; bronchogenic carcinoma.

The understanding of various other abnormal conditions such as patent ductus arteriosus, septal defects, hypertensive, arteriosclerotic, rheumatic, and pulmonary heart disease as well as constrictive pericarditis and chronic pulmonary disease, has been enhanced by angiocardiographic study, although diagnosis in such conditions is usually made without resort to contrast visualization. An attempt has been made in this report briefly to summarize the significant angiocardiographic findings in the above clinical conditions, and to suggest the circumstances under which this method of examination is most productive.

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# POLIOMYELITIS: EARLY DIAGNOSIS AND EARLY MANAGEMENT OF ACUTE CASES \*

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THE title of this paper indicates that it will be concerned with early aspects of diagnosis and therapy. But the adjective *early* should be especially stressed, for, from the standpoint of the acute infection, the early and critical stage of poliomyelitis has heretofore been regarded clinically as the prodromal stage. By the time patients begin to show evidence of paralysis, and often by the time they reach the hospital, it may be late in the disease and the critical period is already passed. Thus according to Russell<sup>1</sup>: "the battle to decide the fate of the spinal-cord cells is probably over before paralysis is detected." There is some experimental evidence<sup>2, 3</sup> to bear this out; and according to Bodian<sup>3</sup> the virus reaches its maximum concentration in the spinal cord some 24 hours before paralysis is detectable, and as paralysis advances, the concentration of virus drops rapidly. We also have learned from the work of Hammon<sup>4</sup> and others, that by the time poliomyelitis patients are admitted to the hospital, the chances are that antibodies to the virus are already present in the blood stream, indicating that infection has been present somewhere in the body for some days.

Before reviewing the clinical picture in this light it may be well to point out that there are certain things about poliomyelitis which are apparently changing, both in respect to its clinical picture and its epidemiology. Primarily we face the fact that the age of the average poliomyelitis patient seen by clinicians in this country is apt to be older than was the case a generation ago. It is clear that the textbook<sup>5</sup> statement made at the turn of the century: "that the disease is rather rare after the age of six," no longer holds. Thus it has become apparent in Scandinavia and in this country, as well as in Canada, in some parts of Europe, and in Australia, that today most of the cases of poliomyelitis in any given epidemic are to be found in children of school age, and in adolescents. In this sense we no longer have "the infantile paralysis." There are certain obscurities about this situation, for, although the percentage of cases in the older age groups has shown a steady increase in consecutive series of cases from certain areas, the contemporary *age specific* rates do not always indicate that adolescent or adult *case rates* are increasing.<sup>6, 7</sup> Nevertheless the fact remains that the average series of poliomyelitis cases in succeeding epidemics within the U. S. contains a decreasing *percentage* of infants and an increasing *percentage* of people over

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15 years of age. No ready explanation for this shift in the behavior of the disease is available, other than it is in part due to shifts in the age composition of the populations involved. But regardless of the explanation, the implication is clear. We should turn our attention more to the clinical picture of *adult poliomyelitis*, now that it is becoming more common.

Another change is that the per cent of those cases which do not go on to lasting paralysis is apparently on the increase. This may be more apparent than real and actually due to the fact that the non-paralytic cases\* have merely received more clinical attention than they did before. In any event, in the 1916 epidemic in New York City, *non-paralytic cases* amounted to about 13 per cent of the total cases<sup>8</sup>; whereas in 1935 in that same city, 33 per cent were recorded as having no paralysis.<sup>9</sup> More recently (1947) we have seen epidemics labelled as poliomyelitis in the middle Atlantic states, in which this percentage has gone up to 70 per cent or above, indicating that but a small fraction of the cases were paralytic.

Here again the explanation for this apparent increase in cases which do not go on to paralysis and yet are called poliomyelitis, is lacking. But regardless of the explanation it is clear that clinicians are called upon today to consider relatively more cases of non-paralytic poliomyelitis than did the preceding generation of physicians. Actually the increase in non-paralytic cases does not make the physician's task any easier in the earliest stages of the disease. For who can tell which cases will go on to paralysis,—in view of the fact that the early symptoms of abortive and non-paralytic poliomyelitis, and preparalytic poliomyelitis are identical?

If we turn next to the clinical picture of acute poliomyelitis it has been found useful in the past to illustrate this in the form of diagrams (figure 1). Such diagrams have in general been derived from series of childhood cases and yet they will do for purposes of introducing our subject here. Fever, vomiting and headache are common to both early and late phases of the disease and to the non-paralytic and abortive forms. Sore throat, it would seem, is a much more frequent complaint in the first phase than in the second<sup>10</sup> and thus becomes a useful symptom to orient the physician in determining with what stage of the disease he is faced. These early and sometimes transient signs of poliomyelitis, although designated in the past as *prodromata*, are actually critical indications that infection has started. From the very onset of fever the virus may already be in the central nervous system and the patient should be handled accordingly. More definite clinical signs of central nervous system involvement which may be heralded by paresthesias, vasomotor changes and pain in the limbs subsequently progress to the

\* Definitions of the terms *abortive* and *non-paralytic* poliomyelitis are not easily made, particularly in this day and age when extensive muscle testing is carried out by specialists. Definitions used in our own clinic are: that an abortive case is a case of "minor illness" in which no clinical or laboratory signs of central nervous system involvement are detected. Obviously such a diagnosis can only be made during epidemics. The *non-paralytic* case is one in which such signs are present either in the form of stiff neck, or pleocytosis in the spinal fluid, etc., but that by the time three weeks from the onset of the illness has elapsed (the usual time of discharge from a hospital) no paralysis is detectable.

development of stiff neck and stiff back and transient hyperactive reflexes, etc. But these latter are *late* symptoms and signs as far as the progress of the infection is concerned and limited to the second phase of the disease.

In view of the changing aspects of poliomyelitis we find that the diagrams in figure 1, based as they are on the infantile forms of the disease, are inadequate. In particular they do not do full justice to the adult case. This has been borne out by Dr. Horstmann's recent studies made in the large epidemics occurring in this country in 1948 both in North Carolina and California.<sup>11</sup> She has demonstrated that the symptomatology of acute poliomyelitis differs in different age groups. For instance, the *diphasic course*,

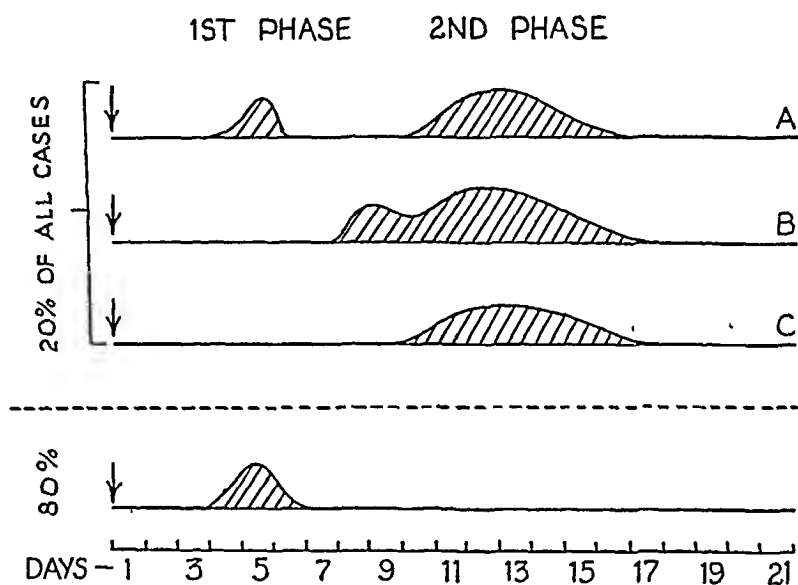


FIG. 1. Schematic diagram of various forms of the clinical picture which paralytic and other types of poliomyelitis may assume. Arrows on the left mark the hypothetical time of exposure to the virus. Forms, A, B and C illustrate both paralytic (and non-paralytic) poliomyelitis, with A as the dromedary type so common in childhood and C the "adult type" with a more insidious onset, and a picture usually limited to second phase symptoms. The lowest diagram is the usual type of abortive poliomyelitis with symptoms limited to those of the first phase. The 80 per cent ratio of abortive to 20 per cent paralytic (and non-paralytic) cases represent arbitrary figures. (From Horstmann and Paul.<sup>10</sup>)

which has already been illustrated as classical, is essentially a manifestation of the disease in children under the age of 10 or 12. It is less common above the age of 14 (table 1). And again the *type of onset* seems to be different in young children from that of older children and adults. Pain in the back and an insidious onset are more apt to occur in patients who are over the age of 15 than under that age. Indeed below the age of 10 the onset of either or both phases is apt to be sudden in 80 per cent or more of the cases, whereas this is true in less than one-half of the cases who are above the age of 15. A gradual onset in an adolescent or young adult may be very puzzling to the clinician and even responsible for a considerable delay in diagnosis. Such cases were seen in the Army in World War II. The type of onset is illustrated in the following case report, which also appears in figure 2.

TABLE I  
Shifts in the Clinical Picture in Relation to the Patients' Age  
(after Horstmann <sup>11</sup>)

Age	No. of Cases	Per Cent of Cases with:		
		Diphasic Course	Pain as an Early Symptom	Gradual Onset *
2-4	83	35	40	18
5-9	105	38	46	18
10-14	78	17	40	44
15-19	58	10	76	53
20+	59	12	76	66

\* This refers, insofar as can be determined, to the onset of the *second* phase.

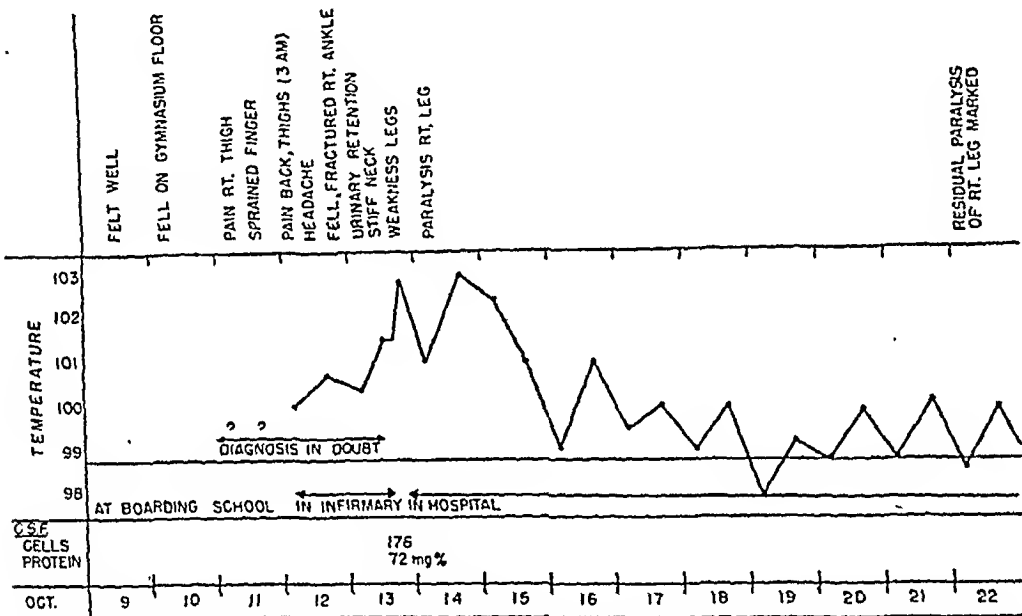


FIG. 2. Temperature chart of J. J., age 17, illustrative of the adult form of paralytic poliomyelitis with a gradual onset.

### Case report of J. J., age 17, a pupil at a boarding school:

His illness occurred during a period when poliomyelitis was not epidemic in the local community. He was well on October 10 until he sustained a severe fall on the gymnasium floor. He was badly shaken and said he never felt "quite right" after that. On the following day he sprained his finger at football practice, but was able to continue playing football. On that night he awoke at 3:00 a.m. with a very severe pain, low down in his back, and made his way over to the school infirmary. His temperature was 100° at this time. Although numerous analgesics including opiates, were administered, this pain persisted all day during which he complained bitterly, and was very apprehensive. Fever was not appreciable at this time, remaining a little above 100°. The diagnosis was sprained back. On the following night, he got up out of bed in the dark to "relieve the pain," and fell. In the morning it was discovered that he had fractured his right fibula. During this period the low back pain continued. By mid-day of the next day (Oct. 13) his temperature had risen to 101°. Previously an orthopedist was called to look at the fracture. There seemed to be some stiffness

of the neck. At the same time, it was found that the patient could not void. The deep reflexes of both lower legs were increased at this time and there was a feeling of numbness in the left leg. He was removed by ambulance to the hospital some 25 miles away, still complaining bitterly of back pain, and by the time he was admitted his left leg was weak. The pain let up on the next day although fever continued and by this time severe paralysis of both legs had developed. At the time he was discharged from the hospital six weeks later, there was very little return of function to the legs. Paralysis of the bladder lasted for about four days, which was also the duration of his febrile period.

Such cases as that of J. J. have in the past been called the "straggling type" of poliomyelitis, a rather poor name but it illustrates the fact that the patient drags along for a few days with the diagnosis in doubt, and he may be subject during this prodromal period of his disease to a certain degree of exertion and trauma which according to Russell <sup>12, 1</sup> and others <sup>13</sup> exert a deleterious effect on the subsequent course of the disease. It is not clear just where the "straggling type" fits into the diagrams of the clinical picture of cases of poliomyelitis but it is compatible with form C in figure 1. It would seem that the first bout of fever, so common in the childhood case, is often absent in the adult case of this type, which begins rather insidiously by developing *second phase* symptoms such as stiffness of the limbs, paresthesias, transient sensory changes, and restlessness and pain, particularly pain in the back. These symptoms are responsible for many erroneous preliminary diagnoses, such as sprained back, renal colic, ruptured disc, etc.

Points in physical diagnosis of the second stage probably need not be repeated here. They center upon the appearance of pain or stiffness of the neck or back, pain in the limbs, and tightness of the hamstring muscles. The spine sign, the head drop, and observation of the abdominal, spinal and other reflexes are all important diagnostic tests. Early lumbar punctures may be helpful, but if there are no "central nervous system signs," the spinal fluid will usually be negative. A point of emphasis here is that, in spite of the fact that careful observation of these patients is strongly indicated at this stage of the disease, if one continually and repeatedly submits the patients to exhausting physical examinations and muscle tests, not to speak of multiple lumbar punctures, an element of exertion or trauma is introduced which is of no benefit to a patient who may be in a highly critical stage of his disease and who even may be hanging in the balance as to whether the virus will produce enough damage in the nervous system as to give rise to paralysis.

It is in this stage of *gradual* onset that the adolescent or adult patient may expose himself or herself to considerable strain on his own volition. It is not uncommon during the early days of poliomyelitis to see a patient who is restless and uneasy and feels driven to exercise or to go out and do things, in order to "shake off" a feeling of insecurity, stiffness or restlessness. The patient may even seek relief by walking the floor half the night or even attending a dance. Sometimes his pain at this stage is severe. Under such circumstances it is not relieved by mild analgesics. But in any event it is well to reiterate that, according to the estimates already mentioned, trauma



or exertion in these early days should be avoided and if the estimates are correct this protection of the patient becomes one of the most important therapeutic contributions that the doctor can make. In schools and camps, athletic directors should be aware of this fact, when poliomyelitis is about.

*Management of Cases.* One cannot be didactic about the treatment of poliomyelitis cases and particularly the treatment in the earliest stages. During epidemic times no clinician, however wise and experienced, can determine during the first few hours or days whether a given case in which the initial symptoms are limited to sore throat, headache, fever and vomiting will or will not go on to the eventual development of paralysis. But the clinician's responsibility with regard to the management of patients of any age who may be in the early stages of abortive or paralytic poliomyelitis seems clear. Thus all individuals with brief febrile illnesses during an epidemic of poliomyelitis should be regarded with suspicion, their physical activities should be curtailed and they should be treated more cautiously than usual and kept under observation for some 10 days. There is another reason why such cases deserve special consideration and why their activities might well be confined, which is, that regardless as to whether or not patients exhibit clinical signs of central nervous system lesions, there is a theoretical public health aspect to the non-paralytic case. For the degree of paralysis or the severity of central nervous involvement apparently bears no relationship as to whether or not the patient will excrete virus in his mouth or intestinal tract. It is not necessary for the attending physician to make a *public diagnosis* of poliomyelitis in order to observe a suspicious case for a week or 10 days. Indeed the physician may not even care to mention the possibility of poliomyelitis to the family, for families are prone to be apprehensive to the point of hysteria during an epidemic and anything which minimizes commotion is desirable. The local health officer may also object if the diagnosis is made too freely or made in the absence of orthodox diagnostic criteria. But this caution does not detract from the desirability of *observing* early and questionable cases most carefully for the development of "second phase" signs, and of regulating their physical activity.

The question as to whether *all* non-paralytic poliomyelitis cases should be hospitalized also raises interesting and controversial points. I am inclined not to recommend it for all patients although a tendency exists in some areas of this country at present to urge the hospitalization of all patients in whom a diagnosis of poliomyelitis (whether suspected or definite) has been made. And yet it is hardly necessary to point out that there are two views and in the event of an epidemic, one should not fill hospital beds with mild cases and thus exclude those who really need hospitalization. My own feeling is that the decision as to whether mild, non-paralytic patients may be best observed at home, will vary in different places and in different epidemics, depending upon the local facilities available for hospitalization and on the facilities for observing the patient at home. A special isolation hospital is not necessary for poliomyelitis patients. General hospitals can care for them

and should accept their community responsibility to do so. It is our belief that ordinary common sense isolation precautions should be carried out in connection with these patients but extreme precautions are not necessary. It has seldom been our experience to observe the spread of poliomyelitis within hospitals. The handling of the patients' stools in the same fashion as typhoid stools are handled is probably not indicated.

As for specific therapy,—there is none. Antiserum, chemotherapy, antibiotics—none of them seem to offer any help in the treatment of the acute poliomyelitis patient at present. The pain at the onset although it may be severe does not usually last very long. Strong analgesics are not very effective in the control of this type of pain and they would seem to be contraindicated. The application of moist heat remains as the most practical method of combating pain.<sup>14</sup> With its use, adequate fluid and salt intake should be kept up. I have had little direct personal experience with the use of prostigmin and of curare but would be inclined to regard them both as being still in an experimental stage. Any physician who has much to do with the clinical responsibilities in this disease knows full well of the pressure which is brought to bear by parents and well meaning friends, to do something definite, something positive or even new and spectacular in the way of treatment. My own feeling is that all meddlesome forms of therapy should be avoided because of their potential traumatic effect. Therapy which includes the use of strong purgatives seems contraindicated.

It will not be the function of this paper to consider the technical aspects of applying moist heat to combat pain and stiffness of the limbs and trunk.<sup>14</sup> That is a special chapter. Nor will it be my function to consider the changing concepts in the care and handling of paralyzed limbs or various other aspects of the paralytic form of poliomyelitis. Much of this aspect of therapy falls within the province of the orthopedist and belongs in the category of the after-care.<sup>15</sup> There are the special problems which occur with the bulbar form of the disease, in which the air passages must be kept as free from secretions as possible by postural drainage, suction, and, as a last resort, tracheotomy.<sup>16</sup> There are also special problems with respiratory paralysis which require the use of the respirator, and there are special problems with bladder paralysis. All require special types of handling.

A final point deserving emphasis is that during epidemics at least, it is expected that a *team* may be required for the proper handling of poliomyelitis patients. This team may be composed of an orthopedist, a physiotherapist, specially trained nurses, and others. In this team the physician must occupy his rightful place as captain during the early stages of the clinical course. He should not resign his captaincy until the case has definitely gone into the stage of after-care, and all the way through he should be on the alert to guard his patient from unnecessary trauma, exertion and above all from meddlesome therapy. The early therapy of poliomyelitis calls for an alert physician whose major responsibility is to guard his patient and to be ready for any serious emergencies.

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# THE DIAGNOSIS AND MANAGEMENT OF ATYPICAL OR VIRUS PNEUMONIA \*

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PRIMARY atypical pneumonia, or, as it is frequently termed, "virus pneumonia," has now become well-defined and established as a clinical syndrome. While it is probably not a new disease entity, it came into particular prominence in 1938<sup>1, 2, 3</sup> following the introduction of sulfapyridine. This drug proved to be effective in the treatment of the true bacterial pneumonias, but not of other kinds of pneumonia, variously termed atypical bronchopneumonia, acute pneumonitis, atypical pneumonia, virus pneumonia, etc. The subsequent sulfonamide derivatives, and, more recently, penicillin, served further to differentiate the bacterial pneumonias from the syndrome now termed "primary atypical pneumonia," since these therapeutic agents were ineffective in the latter disease. Interest in and knowledge of this disease were heightened during the War to such an extent that approximately 300 papers dealing with the subject have appeared in the medical literature during the past 10 years.

It is therefore necessary only to summarize the generally accepted clinical picture of primary atypical pneumonia,<sup>4, 5, 6, 7</sup> before considering certain aspects of the diagnosis and management of these cases.

Primary atypical pneumonia may be described as an acute respiratory infection that begins gradually and insidiously with complaints of symptoms referable to the upper and lower respiratory passages, or of constitutional symptoms such as headache, feverishness, chilliness and malaise. Cough is generally prominent and the sputum is mucopurulent, without blood. On physical examination, the indication of pneumonia is characteristically the presence of medium moist râles in the absence of signs of true consolidation. Radiographically, the pulmonary infiltration is variable in extent, but is often greater than either the patient's appearance or the physical signs in his chest would suggest. The total leukocyte count and differential ratio are usually within normal limits. Pathogenic bacteria commonly causing pneumonia are absent. The course is variable, yet benign; the fever is moderate and of either sustained or remittent character, and the pulse and respiratory rates are relatively low. The duration of illness is usually not more than two or three weeks and recovery is complete, without complications. In approximately one-half of the cases cold hemagglutinins and agglutinins for streptococcus MG appear in the sera during convalescence.

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Epidemiologically the cases tend to occur sporadically, and case-to-case spread is seldom apparent. There is generally a seasonal rise in incidence during the winter months in association with an increase in the total respiratory disease rate. Some evidence indicates that the incidence varies from year to year in different geographic areas.<sup>8,9</sup> The behavior of the disease suggests that the causative agent may induce pneumonia in only a small proportion of the infected individuals, the larger proportion suffering merely from a mild respiratory illness. No reliable figures giving the true incidence of primary atypical pneumonia in large civilian populations are available, but the attack rate in military forces during the past War averaged approximately 10 per 1,000 per annum, exceeding by almost 10 times the incidence of pneumococcal or bacterial pneumonia.

This brief description obviously presents the average or median characteristics of primary atypical pneumonia and neglects the extremes. One of the interesting and at times puzzling features of the disease is the variability of the infection, not only in severity, but also in the clinical features presented by many patients. It may simulate bacterial pneumonia, Q fever, and a variety of other pulmonary infections, as well as neoplastic diseases of the lung, pulmonary edema, and other non-infectious processes. It may take the form of a prolonged, low-grade infection or of a short, acute illness terminating almost abruptly. In other instances, neither a diagnosis of primary atypical pneumonia nor of other known disease processes can be established. The following cases illustrate some of the variations and the resulting diagnostic problems.

The first patient presents a problem in the differential diagnosis of pneumococcal pneumonia and primary atypical pneumonia (figure 1). He was a 43 year old white male who was admitted on the third day of an acute illness initiated abruptly by a shaking chill, and characterized by fever, pleural pain in the right chest posteriorly, and mucopurulent, slightly blood-tinged sputum. He had had a mild cough for one month and had suffered from asthma for 10 years.

On admission the patient did not appear to be seriously ill. His respiratory rate was 20. There were signs of true pneumonic consolidation over the area of the upper portion of the right lower lobe. The total leukocyte count was 12,300, 86 per cent of which were neutrophils. The type III pneumococcus was isolated from the sputum by mouse inoculation, although it could not be found on direct examination (Quellung). Sulfadiazine was administered because of presumed sensitivity of the patient to penicillin. On the ninth day of illness pleural pain appeared in the right chest anteriorly in association with extension of the infiltration to the right middle lobe. The leukocyte count rose to 22,600, of which 90 per cent were neutrophils. Penicillin therapy was instituted. The temperature gradually declined to normal. Serological studies revealed a cold hemagglutinin titer of 256 on the third day of illness, a titer of 512 on the tenth day, and a subsequent fall to levels of 32 and 64. Agglutinins for streptococcus MG failed to develop.

Sera obtained on the tenth and eighteenth days of illness protected mice against 100 minimal lethal doses of pneumococci, type III.

The diagnosis of this illness cannot definitely be established. The physical signs were those of pneumococcal pneumonia, yet the patient's general appearance and his course were more characteristic of primary atypical pneumonia. The laboratory findings likewise are not conclusive. The presence of small numbers of type III pneumococci in the sputum does not establish this illness as pneumococcal pneumonia, particularly since the type III pneumococcus is one of the common carrier types. The patient may have suffered from primary atypical pneumonia, from pneumococcal pneumonia, or, possibly, from both diseases.

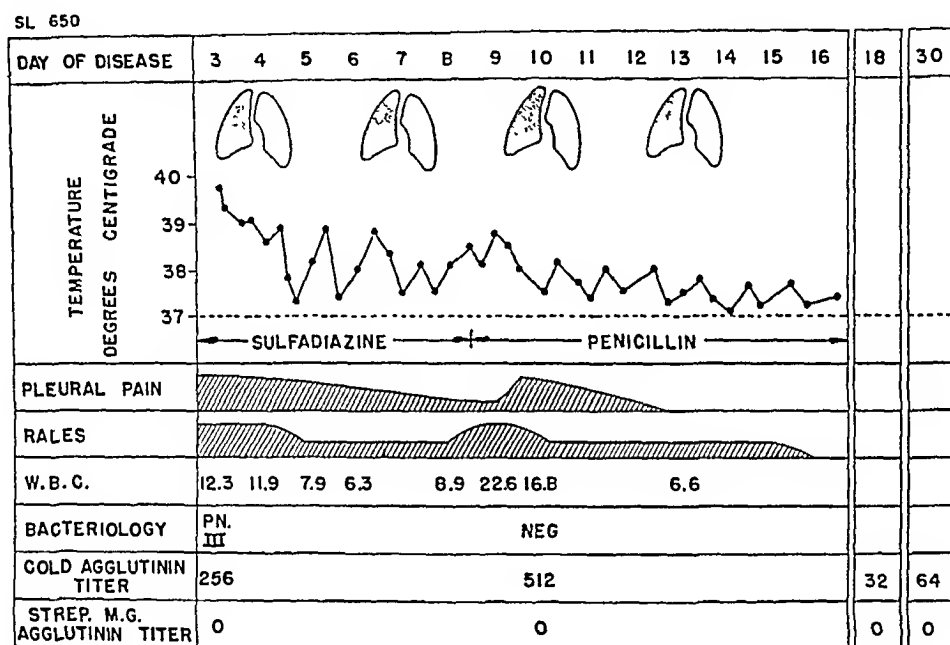


FIG. 1. Clinical chart of a patient whose illness illustrates the problem of differential diagnosis of primary atypical pneumonia and pneumococcal pneumonia.

The next two patients illustrate both the diagnostic problem and the prolonged, low-grade nature of "atypical pneumonia" in the older age group. One of the patients (figure 2) was a 70 year old white female who became ill rather suddenly two weeks before admission. The first symptom was a moderately severe cough productive of gray, mucopurulent sputum. Weakness, fatigue, low-grade fever and gradually progressive anorexia ensued. Penicillin was ineffective. On admission, physical examination revealed medium fine râles at both bases posteriorly and roentgenogram showed infiltration of the left lower lobe. The course was characterized by a slow and gradual improvement not influenced by therapy with aureomycin.\* No pathogenic bacteria were isolated. Neither cold hemagglutinins nor ag-

\*Furnished by the Lederle Laboratories Division of the American Cyanamid Company.

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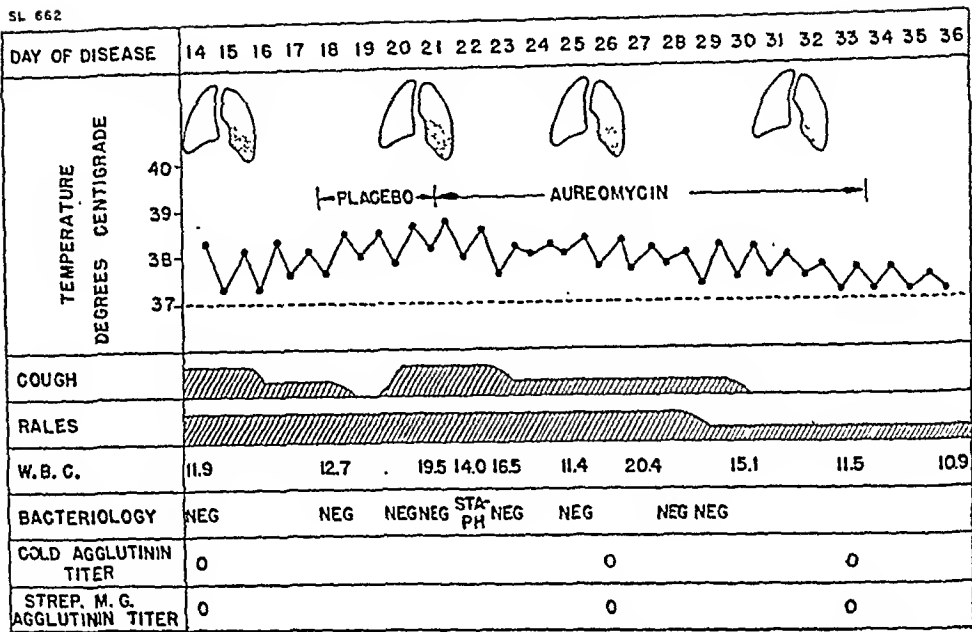


FIG. 2. A prolonged, low-grade type of primary atypical pneumonia in an elderly patient whose illness was not influenced by therapy with aureomycin.

glutinins for streptococcus MG developed. No underlying organic disease was detected.

The other patient (figure 3) was a 69 year old female whose illness began with a productive cough three weeks before admission and was characterized by fatigue, mild malaise and low-grade fever. On the day before admission she had a severe bout of coughing and wheezing attended by marked respiratory distress. Penicillin was administered on the day of admission.

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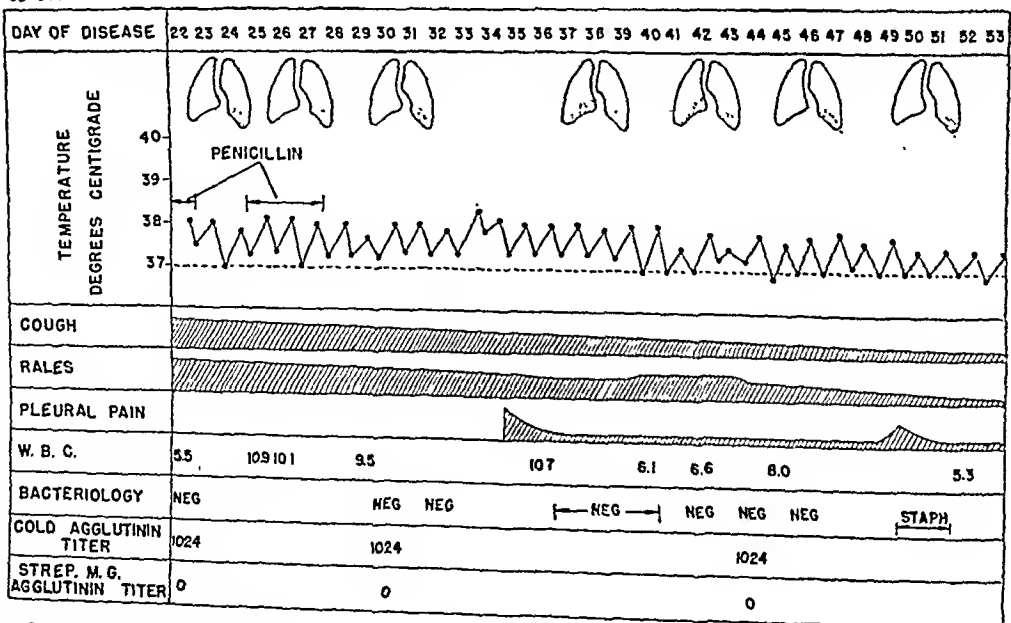


FIG. 3. A prolonged, low-grade type of primary atypical pneumonia in a 69 year old woman.

Physical examination on admission revealed coarse and sibilant râles throughout the chest and medium fine râles in both lower lobes. Fine râles were later heard over the left upper and right middle lobes, associated with apparent spread by roentgenogram. Pleural pain and a friction rub appeared over the right middle lobe on the thirty-sixth day, and gradually subsided with an exacerbation on the fiftieth day. Penicillin was without effect. A cold hemagglutinin titer of 1,024 persisted throughout the hospital stay.

Presumably both of these patients illustrate a prolonged and low-grade form of primary atypical pneumonia. In one instance cold hemagglutinins were absent, in the other a high titer had developed by the end of the third week of illness. Neither patient harbored the pathogenic respiratory bacteria commonly associated with bacterial pneumonia.

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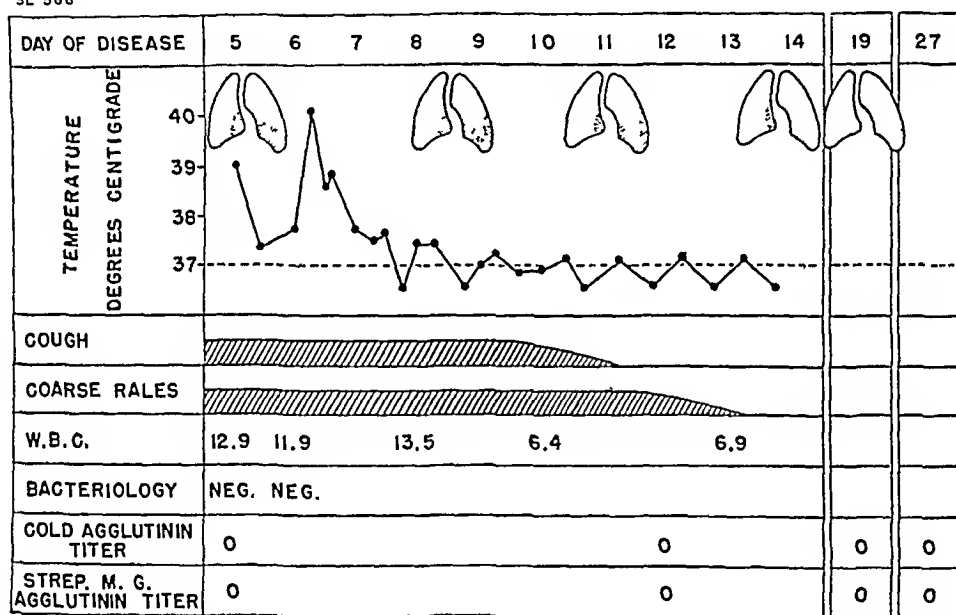
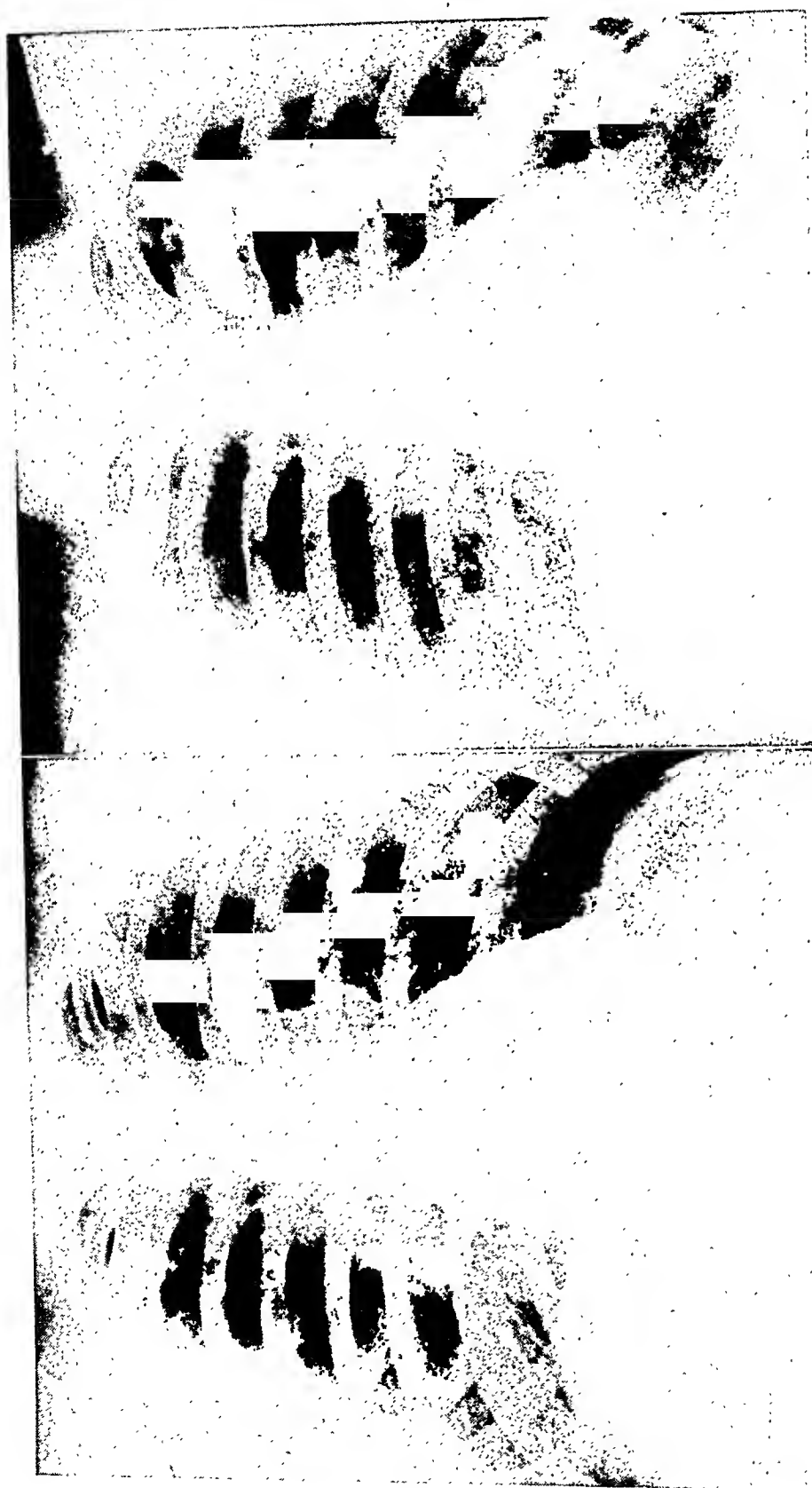


FIG. 4. Moderately severe primary atypical pneumonia in a young adult man whose fever subsided within a period of 48 hours without therapy.

The remaining two cases (figures 4 and 5) are presented to illustrate the opposite extreme in variation. In both of these patients the illness was moderately severe and of approximately a week's duration. In both defervescence occurred sharply over a period of 48 hours and the temperature remained at a normal level during convalescence. In other respects, however, the illnesses conformed to the general picture of primary atypical pneumonia.

Differential diagnosis of primary atypical pneumonia therefore requires an appreciation of the great variability in the infectious process as well as of the variety of causes of this clinical syndrome. There is as yet available no specific laboratory test, based on the causative agent, to give direct confirmation of the diagnosis of primary atypical pneumonia. Nor is there





June 7  
3rd Day

June 10  
6th Day

FIG. 5. Moderately severe primary atypical pneumonia in a young adult male whose febrile illness terminated rather abruptly during a period of 48 hours.

conclusive evidence that only a single agent, presumably a virus, is responsible for these cases. A reasonably certain diagnosis can be established only by excluding other causes for the illness, both infectious and non-infectious. The list of such infectious agents is long and includes bacterial infections, such as tuberculosis, tularemia and the bacterial pneumonias; fungous infections, such as coccidioidomycosis; rickettsial infections, such as Q fever; parasitic infections, such as schistosomiasis; and virus infections, such as influenza, psittacosis, and lymphocytic choriomeningitis. Non-infectious causes include pulmonary edema with or without heart failure, pulmonary infarction, atelectasis, neoplasms, sarcoidosis, etc. Considering the over-all occurrence of the syndrome, however, these known causes account for only a

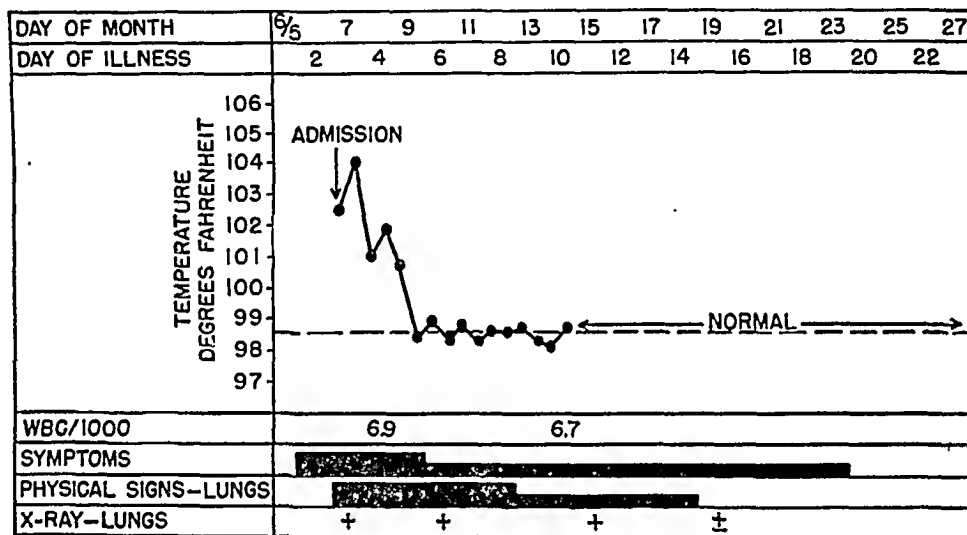


FIG. 6. Moderately severe primary atypical pneumonia in a young adult male whose febrile illness terminated rather abruptly during a period of 48 hours.

relatively small proportion of the total number of cases and a definitive diagnosis can be reached in most of them. The remaining cases, now considered as primary atypical pneumonia, are numerically most important and will be encountered most frequently. It is highly important, however, to keep the differential possibilities in mind with each individual patient, especially in view of the rapid development of new therapeutic agents.

The general symptomatic and supportive care for patients with primary atypical pneumonia is well known. Only two aspects of the management of this disease will therefore be considered here, namely, the questions of isolation and of specific therapy.

Epidemics of primary atypical pneumonia and case-to-case spread of the infection are infrequent, but they have been observed, particularly in institutions, schools, and among the staffs of hospitals.<sup>3-7</sup> A few instances of multiple cases in a family have been reported.<sup>3,7</sup> During the winter of 1947 to 1948 in Cleveland, Jordan<sup>10</sup> observed 19 families in which multiple cases of atypical pneumonia and associated respiratory infections occurred, apparently as the result of household spread. Of the 83 persons in these

families, 60, or 73 per cent, had a respiratory infection and 29 of these were established as primary atypical pneumonia. Because of such examples of apparent contact spread, the question is frequently raised as to the need for isolation. From the evidence now available, however, there is little reason to believe that isolation would be effective in most circumstances, with the possible exception of a hospital in which epidemic spread is occurring. The great majority of cases still occur in a sporadic manner. The incubation period is long, approximately two to three weeks, and the period of infectiousness has not been defined. Moreover, the frequent occurrence of mild, non-pneumonic forms of illness probably due to the same agent indicates that isolation of only those patients with pneumonia would have little effect on the spread of the infection. At the present time, therefore, it seems reasonable to continue to handle these cases without strict isolation precautions.

The question of specific therapy in primary atypical pneumonia is now in the process of reëvaluation. The efficacy of any therapeutic agent has been and continues to be extremely difficult to determine, because of the variability of the clinical course and the difficulty of establishing a firm diagnosis by the laborious methods of exclusion. For these reasons the failure of an agent to alter the course of illness and to prevent spread of infiltration in a few patients is probably more indicative of the true worth of the agent than is apparent success in a larger number of cases, as Finland, Collins and Wells<sup>11</sup> have emphasized.

Convalescent sera and gamma-globulin have been used to a limited extent for therapy of primary atypical pneumonia.<sup>7, 9, 12-15</sup> These agents have not been evaluated adequately, but it seems probable that they are not very effective.

Sulfonamides, and likewise penicillin, have generally been found to have no effect on the course of the infection. In cases where the diagnosis is in doubt, however, it is advisable to administer penicillin after the diagnostic procedures have been carried out. The lack of a definite response within 72 hours is usually an indication to discontinue the drug unless a bacterial etiology has been established. The administration of sulfonamides or penicillin is frequently suggested for the prevention of secondary bacterial infections. If the diagnosis of primary atypical pneumonia is reasonably certain, the value of such therapy is very questionable. Secondary bacterial infection is an extremely rare complication, occurring less frequently than toxic reactions to the drugs. Its occurrence, moreover, is usually obvious clinically and can be readily confirmed before or coincidental with the administration of specific therapy at that time.

There are few reports of the use of streptomycin in the treatment of primary atypical pneumonia, although this antibiotic agent is generally thought to have no effect on the course of the disease. Finland, Collins and Wells<sup>11</sup> have reported two cases in which defervescence and clinical improvement followed promptly upon administration of streptomycin. Further data are needed to permit evaluation of this agent.

Recently, three groups of investigators have reported the treatment of primary atypical pneumonia with aureomycin.<sup>11, 17, 18</sup> The three series were not controlled, but comprise 43 cases reported in detail, of which 42 showed clinical improvement within three days after administration of the drug. The diagnosis was supported in the majority of the cases by the development of cold hemagglutinins. These results are highly encouraging, despite the difficulties of evaluating therapy in any individual patient. In view of the great variability of the disease, however, it is essential that further critical trials, and, if possible, controlled studies, be carried out before aureomycin is accepted as a specific remedy for primary atypical pneumonia.

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# SYNCOPE: A REVIEW \*

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## INTRODUCTION

THIS discussion of syncope is divided into three parts: first, a brief consideration of the subject, second, a description of the various syndromes, and third, a review of some biological aspects of the reaction in certain instances. The work of Weiss and his associates <sup>1</sup> forms the basis of our present knowledge; his classical review in the *Oxford Medicine* was written about 1937. Since then the chief contributions have come from Engel and Romano <sup>3,6</sup> who have not only utilized the relatively new technic of the electroencephalogram, but have also studied fainting from a modern psychological point of view.

Fainting is so common that we tend to disregard it; so it is well to point out at the onset that transient benign syncope and fatal syncope are probably based on the same mechanisms. Instantaneous death is not uncommon, but at autopsy we rarely find anything to explain it. Evidence of chronic structural abnormalities is often found, particularly in the heart, but such abnormalities are not incompatible with life and are found frequently when they did not contribute to the cause of death. Thus the evidence points towards the concept that instantaneous death is often fatal syncope, ventricular fibrillation or asystole of various types. Moritz <sup>2</sup> has made the interesting suggestion that the so-called thymo-lymphatic deaths are probably instances of fatal syncope due to hypersensitivity of certain reflexes.

In normals the sensitivity of reflexes may vary strikingly, and in disease it may be markedly increased. This applies to both physical and functional diseases. Likewise, in disease the compensatory recovery mechanisms following reflex changes may be slow or may fail altogether. Such increased sensitivity may occur at either end of the reflex arc and possibly at the site of the central connections. Little is known about the reactions at the sensory end of the arc, but at the motor end a few of the changes involved in translating the neuro-chemical impulse into muscular or glandular response are now understood to some degree. The acetylcholine-choline esterase system is perhaps the best known example.

Syncope collapse and shock should be considered as a continuum rather than as separate entities. The common denominator is best described as a discrepancy between the volume of the circulating blood and the capacity of the vascular bed. This concept holds for all the cardiovascular types of syncope. A review of the factors producing such a discrepancy suggests a

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rough separation into those involving primarily the pumping apparatus and those involving the pipe line system. Pumps fail from troubles in rate, in valves, and in output of power. A group of pipe lines contained in a housing of some sort may leak to the outside or may leak into the spaces between the pipes, or the number and size of functioning pipes may be increased or decreased. Thus capillaries may shut down entirely, or they may dilate to some two and one-half times their usual normal size. This last possibility reminds us that biological plumbing, like modern plumbing, is complicated by intricate electrical control devices, and in the majority of syncopes due to pump or pipe line troubles we find the nervous system involved. And further we discover that in some instances the pump and pipe lines are not involved at all, the trouble being solely in the electrical system. This then forms the basis of a tentative classification. Its value is slight; it serves merely to orient us in the attempt to make order out of chaos.

### 1. Electrical:

1. Hypoglycemia.
2. Epilepsy.
3. Hysteria.

### 2. Pump:

- Rate: 1. Tachycardia.  
 2. Adams-Stokes syndrome.  
 3. Reflex—vagus to vagus (so-called vago-vagal type).  
 4. Reflex—carotid sinus to vagus.

Valves: 5. Valvular damage.

Motor: 6. Myocardial weakness.

### 3. Pipe Lines:

1. Reflex—psyche to peripheral vascular bed (vaso-vagal or vaso-depressor type).
2. Reflex—carotid sinus to peripheral vascular bed, and to cerebral vascular bed.
3. Postural hypotension (normal reflex failure).
4. Collapse and shock.
5. Miscellaneous rarities.

## DESCRIPTION OF SYNDROMES

It is not the intention that this review should be a German "Handbuch" with detailed pictures of the various syndromes. These are available in the literature. Exceptions will exist to many of the general statements which follow because of the frequency of complicating factors in many types of syncope. Such omissions are justified because an overall picture of syncope is our immediate purpose.

A. Syncope due to electrical trouble without involvement of the pump or pipe lines.

1. *Hypoglycemia*. This is included as a sop to tradition. The respiratory quotient of brain tissue is 1, suggesting that only sugar is metabolized. Oxygen consumption of the brain has been shown to be markedly reduced during unconsciousness due to hypoglycemia. We assume, therefore, that the decrease in oxidation of carbohydrates does not allow sufficient chemical activity to support consciousness.

2. *Epilepsy*. Faints and fits are notoriously hard to tell apart. It is generally stated that faints have cardiovascular involvement, no aura, occur in the upright position, have no associated convulsions, are followed by prompt recovery and are not apt to recur. And it is generally stated that fits have a neurogenic etiology without cardiovascular signs, have an aura, occur in any position, have associated motor phenomena, are followed by subsequent confusions and are apt to recur. These statements hold true in the majority of instances but there are exceptions. Faints may be accompanied by such phenomena as auras, convulsions, micturition, defecation, injuries, and subsequent confusion. They may recur, and they may occur in the horizontal position. Likewise fits may be accompanied by little or no convulsive movements, there may be marked vasomotor changes, and emotions may precipitate them. Thus the differential characteristics are relative and not absolute. Electroencephalograms are a great help in sorting out these borderline states.

3. *Hysteria*. We are indebted to Engel and Romano<sup>3</sup> for their recent delineation of this syndrome. Practically all types of fainting we will consider, except this one, involve the cardiovascular system, are due to cerebral anoxia, and show electroencephalographic changes. Here, however, the usual muscular and vascular symptoms preceding the common faint are absent. The subject loses consciousness in an abrupt and dramatic manner with no cardiovascular changes, no respiratory changes, and no electroencephalographic changes. This type of fainting occurs more frequently in women, and is often but one of several hysterical manifestations. It usually occurs when the subject is in the presence of others, no injuries are sustained from a fall, and unconsciousness may persist for as long as an hour or so despite a prone position. Its actual incidence is not known but it is probably much less common than the usual vascular type of fainting.

For those who struggle with psychosomatic terminology this is an important syndrome because it is purely psychological; it is an hysterical symptom in pure culture. On the other hand the usual faint has associated cardiovascular changes and is an organ neurosis. The basic cause of the usual faint is equally psychological but the mechanism of production of the symptom is different, involving the autonomic nervous system and measurable physiological changes. These two types of fainting, pure conversion hysteria and pure organ neurosis, have been considered as representing the two ends of a spectrum, whereas many of our psychosomatic illnesses fall

somewhere in between and represent mixtures of varying degree of hysteria and organ neurosis. Few clinical syndromes allow of such clear delineation and objective proof as these two types of fainting.

B. Syncope due to pump troubles. These cardiac disturbances may be due to disease processes within the heart, or to reflexes reaching the heart via the vagus, or to a combination of both factors.

1. *Tachycardias*. There is little to say about this group. It is well known that under these circumstances the pumping action of the heart is highly inefficient. Of a hundred reported cases, 15 had cerebral symptoms. This included four cases of syncope, two of which had convulsions.

2. *Adams-Stokes syndrome*. This term is used in its commonly accepted meaning of damaged conduction system with partial or complete heart block. If the block is partial the attack of syncope is usually due to the sudden onset of complete block with delay in formation of the idioventricular pacemaker. If the block is complete the attack may be due to one of several changes, a temporary inhibition of the ventricle pacemaker, a sudden shift in the location of this pacemaker with a further reduction of an already slow rate, or transient runs of premature ventricular contractions. The degree of existing cerebral sclerosis is important here as evidenced by the fact that anywhere from 3 to 15 seconds of asystole may be required to produce syncope. It is the function of the total cardiovascular apparatus in oxygen transport that counts, and not the heart rate. A rate of 30 is perfectly compatible with health, but a sudden change to a rate of 30 may produce syncope because compensatory reactions occur too slowly to maintain an adequate cerebral circulation. As is well known, ephedrin increases ventricular irritability and markedly reduces the frequency of attacks.

3. *Reflex*—vagus to vagus (so-called vago-vagal type). This is a most important group because it contains the fatal and often preventable syncopes. The afferent limb of the reflex arc may be anywhere in the wide area served by the sensory component of the vagus. The efferent limb consists of the motor fibers in the vagus which run to the heart. The result of impulses transversing this arc is a sudden change in cardiac rate. This type of syncope due primarily to vagal cardiac inhibition has been called Adams-Stokes syndrome of reflex origin. It is true that this title is historically justified, because both Adams and Stokes described cases in which the heart rate suddenly slowed to the extent that the patient fainted. The actual mechanisms in their cases will never be known. However, our thinking will be clearer if we follow common usage and the dictionary, and restrict this somewhat obnoxious title to syncope associated with organic heart block. The specific effect of vagal inhibition on the heart varies tremendously. Some order can be made of it if we consider the three possible sites of impulse formation, the SA node, the AV node and the ventricular conduction system. In any of these areas impulse formation or impulse transmission may be slowed or stopped altogether, and in two of them fibrillation may possibly be initiated. Thus we have SA slowing, SA block and possibly auricular fibrillation, AV



slowing, AV block, and ventricle slowing, ventricle block and ventricle fibrillation.

A well known example of this reflex arc is so-called pleural shock. A controversy formerly existed as to whether this syndrome was due to reflex changes or to air embolism. The latter theory was discarded because of the following points: (1) experimental work favors the reflex theory, (2) the unilateral neurological signs sometimes seen in pleural shock, and called on to support the air embolus theory, are also seen in the cerebral type of carotid sinus syndrome, (3) a very nice bit of clinical investigation has demonstrated that during the performance of initial pneumothoraces a fall in blood pressure and pulse rate occurs only as the needle encounters the unanesthetized parietal pleura. Anesthesia of the pleura or a prior injection of atropine abolishes this vascular response. Pleural shock has occurred under many circumstances such as chest taps, irrigation of cavities, moving of drains, and blows on the chest wall. Mechanical irritation such as needling has been shown to give a more intense reflex if the pleura is inflamed.

The afferent limb of this reflex arc may arise in the esophagus. Weiss<sup>1</sup> records the case of a man who for 10 years had suffered from frequent fainting on swallowing, and finally was hospitalized after a suicidal attempt. A diverticulum of the esophagus was found, and the syncopal attack, which was due to transient AV block, could be reproduced by the distention of a balloon in the esophagus. Ephedrin abolished the unduly slow rate, atropine abolished the AV block, and eventually a surgeon abolished the diverticulum.

Similar reflexes may arise in the walls of the bronchi, and sudden changes in cardiac rate have been reported during bronchoscopy and at operation. Stimulation of the auricular branch of the vagus is known to produce cough but also may produce syncope. Various procedures during abdominal operations may produce slowing of the heart rate and transient asystole. Such reflexes may arise in the heart itself, and this constitutes one of the problems of cardiology. Many patients with infarctions who survive the initial shock die very suddenly in hours or days, probably with ventricular fibrillation. Quinidine has been advised to diminish ventricular irritability, thus rendering the end organ less susceptible to vagal stimulation, and atropine has been advised to block the reflex arc at the nerve ending. In experimental myocardial infarctions atropine apparently does reduce mortality but data in humans are difficult to obtain.

4. *Reflex*—carotid sinus to vagus. There is no essential difference between this and the vagus to vagus reflexes just discussed. It will be considered later with the two other types of carotid sinus syncope.

5. *Valvular damage*. Advanced valvular heart disease with obstruction, such as mitral and aortic stenosis, and congenital narrowing of the aorta may be associated with syncope on exertion. It would seem that an inadequate cardiac output was at fault but there is evidence to show that reflex factors are present in addition. Cases of aortic stenosis characteristically

die suddenly without demonstrable cause, and this type of death supports the contention that reflex factors play an important rôle.

6. *Myocardial weakness.* Cases of paroxysmal nocturnal dyspnea and acute pulmonary edema due to left ventricle failure may suddenly lose consciousness. Again it is probable that reflex and mechanical factors combine to produce the syncope.

Unfortunately the situation at times is more complicated than this description of a single reflex arc suggests. In the first place our knowledge of the sensory components of the vagus is very scanty and the afferent limb of the arc may sometimes lie in the sympathetic system. In the second place it has been demonstrated that the efferent limb is not solely vagal with resultant cardiac inhibition but may also be sympathetic with peripheral vasodilatation. For practical purposes, however, the chief effect is the vagal one. Therapeutically, it is very important that these patients receive atropine, particularly if they are elderly or nervous, or both. If tolerated 1 mg. (1/75 gr.) is preferable to the usual 0.5 mg. (1/150 gr.).

C. Syncope due to pipe line trouble.

1. *Reflex*—psyche to peripheral vascular bed (vaso-vagal or vasodepressor type). This is the common fainting that is so familiar to all of us, that occurs after prolonged standing or with a venipuncture. The classical swoon of the Victorian lady probably belongs in this category. The fainting results from cerebral anoxia which follows an increase in the capacity of the vascular bed with resultant inadequate venous return and inadequate cardiac output.

The factors affecting this mechanism are numerous and can be divided into physical and psychological. In brief the physical factors include such things as infections, heat, debilitation, malnutrition and anemia, vomiting, first trimester of pregnancy, mountain sickness, instrumentation, inadequate circulation from any cause, paracentesis with resultant pressure changes, chemical factors such as spinal anesthesia or nitrites, and prolonged maintenance of the upright position. The psychological factors consist of the witnessing of accidents, injuries or mutilation, the learning of tragic news, the experiencing of minor surgical procedures including venipuncture, suggestion and possibly pain. Pain alone is not an adequate stimulus; we shall see later that pain actually reverses the mechanism.

Fainting can be experimentally produced in susceptible patients by means of a tilt table, or in any subject by means of a tilt table plus emotional stimuli or vasodilating drugs such as sodium nitrite. The associated symptoms and signs are easily studied under such circumstances. They consist of peculiar epigastric sensations, weakness which soon becomes extreme, light headedness or giddiness, yawning, sighing respiration, pallor, sweating, sometimes headache or tinnitus, precordial discomfort, and hyperperistalsis with attendant cramps, nausea or belching. Sometimes just before the onset of syncope there is a sense of coldness or numbness starting at the periphery and moving centrally. Then the sudden loss of consciousness

occurs followed by convulsions if the subject is not tilted back to the prone position. Nothing so resembles death; the pallor is ghastly and the pulse weak to absent. Just before the onset of syncope the subject may experience anxiety and a fear of impending dissolution, symptoms which remind us of myocardial infarction. Indeed the mechanism of production of such sensations by the autonomic nervous system is probably the same in both instances. Physiologically, the symptoms occur during a period of falling systolic pressure and diminishing cardiac output. The diastolic pressure is maintained, or even rises, which means that the essential change is a diminution in pulse pressure. Meanwhile the pulse rate increases and then just prior to syncope there is the precipitous fall in both blood pressure and pulse rate. The classical bradycardia is a secondary phenomenon because the slowing of the pulse can be prevented by atropine without interfering with the production of the faint. Gravity determines only the final drop in blood pressure as all the other changes may be seen in the prone position. It is important to remember that the reaction may continue long after the stimulus is withdrawn, even for two to three hours.

In the brain no changes are observed by electroencephalogram until unconsciousness occurs; then the normal fine waves are replaced by large slow waves which persist until consciousness is regained.

Despite our habit of discoursing in a learned manner about peripheral vasodilatation the nature of the changes which occur in the peripheral vascular system is not known. All we do know is that the blood ceases to return from this hinterland. It has been demonstrated recently that as much as 1.5 liters of blood may be held in the muscles during syncope. Whether there is active vasodilation in the muscles under such circumstances, or simply passive vasodilation due to vasoconstriction elsewhere, is not known. Finally, the highly important factor of the effect of muscle tonus on the capacity of the venous bed has not been quantitated.

Recovery mechanisms consist of the abolition of the effect of gravity by the fall, by convulsive movements which have a muscle pumping effect on venous blood, and possibly certain other reflexes which arise centrally as a result of cerebral anoxia. Sudden death may conceivably result from the failure of these recovery mechanisms. Engel<sup>3</sup> has demonstrated that following a faint the signs and symptoms are prolonged by lying motionless, but may be reversed by exercising in the prone position. The importance of exercise is also demonstrated by the ease with which syncope may be produced in an athlete by having him stand motionless immediately after violent exercise. Fainting is common during various painful procedures, but in the experimental subject it can be demonstrated that pain tends to reverse the reaction. The time honored remedies of a bucket of cold water, slapping the face, ammonia, and even the Victorian chafing of the wrists have the sound theoretical basis of stimulating sympathetic and muscular activity.

2. *Reflex*—carotid sinus to peripheral vascular bed, and to cerebral vascular bed. Just beyond the bifurcation of the common carotid the internal

carotid artery shows a slight bulging. Here in the arterial wall are specialized end plates affected by pressure changes, and a rich nerve plexus with central connections via the glossopharyngeal nerve. Very close by lies another structure, the carotid body, which is affected by chemical changes in the blood. Two comparable sensory receptors lie in the arch of the aorta. Thus there are the carotid and aortic nerves responding to pressure changes and the carotid and aortic bodies responding to chemical changes. This is the grossest of generalizations but is adequate for our purpose. These end organs constitute important buffers of the cardiovascular system, emergency regulators with a restraining influence preventing undue change, particularly undue elevation of blood pressure and pulse under conditions of physiological stress.

Mechanical stimulation of an unduly sensitive carotid sinus nerve plexus causes syncope by three very different mechanisms. The afferent limb of the reflex arc is the same in each of these three, consisting of the nerve plexus in the wall of the carotid sinus and the glossopharyngeal nerve.

In the first group the efferent limb consists of sympathetic nerves to the peripheral vascular bed with the vasodilatory or so-called vasodepressor effect, the mechanism of which has just been discussed. Ephedrin will decrease this response to some degree.

In the second group the efferent limb is made up of cardio-inhibitory vagal fibers. It belongs, therefore, under the heading of pump troubles. This carotid sinus to vagus reflex occurs chiefly in the elderly arteriosclerotic group. It has been definitely demonstrated that digitalis increases the sensitivity of the reflex, and one should remember this in digitalizing elderly patients. Increasing the irritability of the heart with ephedrin helps to prevent attacks, but blocking the vagus terminals with atropine is much more effective.

In the third or so-called cerebral group the efferent limb of the reflex arc lies in the brain itself and its course is unknown. The attacks occur without changes in blood pressure or in cardiac rate, and atropine and ephedrin are without effect. Induced attacks occur three or four seconds after mechanical stimulation of the sinus, whereas in the other two groups, the lag is from 12 to 16 seconds. No changes can be demonstrated in total cerebral blood flow, but there is now evidence pointing to localized vascular changes in the brain. The same electroencephalographic changes occur as with vasodepressor syncope, but usually they occur only on the contralateral side, although they sometimes may be bilateral and rarely homolateral. This unilateral affect you will remember has also been noted in pleural shock but there its mechanism has not been worked out. This type of carotid sinus syndrome occurs in younger patients who usually show the stigmata of vasomotor instability, such as palmar sweating, palpitation, fluctuating blood pressure, dermatographia, and so forth.

Only some of the factors which produce increased sensitivity of the carotid sinus reflex are known. Instability of the autonomic nervous system

is apparently a factor in the cerebral group. Occasionally organic lesions are present, tumors or aneurysmal dilatation of the carotid artery. Arteriosclerosis seems to increase sensitivity, and digitalis may do so. In days gone by high stiff collars were at times a sartorial hazard. If drug therapy is inadequate in the vasodepressor and vagal types, surgical ablation of the nerve plexus is usually effective.

3. *Postural hypotension* (normal reflex failure). This is commonly seen as a mild fleeting affair in cases of vasomotor instability, and is now encountered following sympathectomy for hypertension. It occurs rarely with spinal cord diseases, such as tabes, which may involve the sympathetic pathways. Normally, when a subject suddenly assumes the erect position both systolic and diastolic pressures rise and the pulse rate rises. Here both mechanisms fail. The pressures actually fall and the pulse rate fails to rise. So far as is known poor vasomotor tone with sudden pooling of venous blood is responsible. Rubber bandaging of the lower extremities is the most effective therapeutic procedure.

The effects of centrifugal force are comparable to those of gravity, and have been extensively studied by aviation physiologists. The well known G is defined as a force equal to that of gravity. The sensations of a person subjected to increasing centrifugal force are as follows:—at 2 Gs the hands and feet feel heavy and there is increased pressure of the buttocks against the seat; at 3 to 4 Gs there is an exaggeration of these symptoms and the head is held up with difficulty; at 5 Gs the subject can hardly move and has trouble breathing, and between 7 and 8 Gs there is the sudden "blackout." Pulse and blood pressure responses have been studied under these circumstances, and a constant lag has been demonstrated of from 10 to 15 seconds between the application or removal of the force and the cardiovascular response. This is comparable to the 12 to 16 seconds lag in the vasodepressor type of carotid sinus syncope, and shows the characteristic time period for the induction of the diminished venous return—diminished cardiac output cycle. The hydrostatic effect at 5 to 8 Gs is such that the usual compensatory mechanisms are helpless. Armstrong<sup>4</sup> reproduces some remarkable serial chest roentgen-rays of a monkey before and during the application of a centrifugal force of 5 Gs. As the force is applied the heart shadow almost disappears, suggesting that venous inflow has almost ceased. Abdominal supports increase the subject's tolerance by  $\frac{1}{2}$  to 1 G, and pressurized suits have a somewhat greater effect. With the increasing air speeds now becoming available this problem is of great importance to the fighter pilot, because it represents the chief factor limiting maneuverability.

4. *Collapse*. This constitutes an ill defined intermediate stage between syncope and shock. Here as in the vasodepressor type of syncope we are concerned primarily with an increased capacity of the vascular bed, rather than with disturbances in the function of the heart. The only differentiating point between syncope and collapse is that in syncope the changes are more sudden and recovery is more rapid. In collapse it is probable that we have

the beginning of the tissue changes of shock, the vicious circles which follow anoxia of the capillary endothelium. Knowledge of the pathological physiology of collapse is hampered by an understandable disinclination to produce this syndrome under experimental conditions in humans. Certain mammals such as rabbits, if tied on a board in the upright position, will go rapidly into collapse and die. Normal human subjects upright and motionless on a tilt table may show the steadily progressing changes previously discussed, which are reversed only by the prone position or by a convulsion following syncope. Were the position further maintained collapse and shock would probably ensue.

In antiquity this human experiment was carried out in the form of crucifixion, and some accurate accounts of the manner of death have come down to us. Apparently bleeding was not an important factor, and in some instances the subjects were tied rather than nailed to the cross. Again, as in the normal human subject on a tilt table, great variability was noted in tolerance. Some died within two or three hours, and this group often exhibited marked thirst which suggests the thirst of shock. It was repeatedly mentioned that when death occurred it was quite sudden, the subject having appeared comparatively strong a few minutes before.

5. *Miscellaneous rarities.* A few very rare types of syncope are worth mentioning because they are so interesting. Cases of polycythemia and obstruction of the superior vena cava may faint at times; cerebral engorgement has been invoked to explain it. Back injuries have been reported to be followed by syncopal attacks, and in such cases loss of tonus in minute vessels of the hands and feet has been demonstrated. Vasodepressor and vagal responses due to central stimulation are seen at times following traumas to the head, either accidental, or purposeful in the form of operations and ventriculograms. A state of collapse is rarely seen following the use of large amounts of procaine for local anesthesia; intravenous barbiturates constitute a highly effective antidote. Syncope has been reported in dissecting aneurysms of the aortic arch, and may be due to mechanical stimulation of the aortic depressor nerve. Syncope of various types may occur rarely with the hyperventilation syndrome.<sup>5</sup> It may be vasodepressor, and due either to the original anxiety producing the hyperventilation, or to anxiety caused by the symptoms of hyperventilation. It may be primarily orthostatic, or it may be hysterical. Prolonged compression of the chest if suddenly released may produce syncope by pooling of the blood in the pulmonary circuit. The Valsalva experiment, a maintained expiratory effort against a closed glottis, may induce syncope by increasing pulmonic pressure to such a degree that the circulation is obstructed.

#### THE BIOLOGICAL MEANING OF COMMON SYNCOPE

Engel and Romano<sup>6</sup> have recently developed a concept of common vasodepressor fainting which embraces the known psychological and physiological

factors involved. They point out that vasodepressor syncope occurs under certain specific circumstances. 1. In healthy people under a wide variety of injuries with or without pain and blood loss. 2. In healthy people under circumstances in which fear must be denied and relative immobility maintained. All the "first time" non-repetitive faints come in this category, the faints that occur on experiencing the first venipuncture, or on witnessing for the first time an autopsy or an operation. 3. In neurotic individuals as a repetitive reaction. From this we see that the bodily changes in fainting represent the physiological concomitants of an emotional state, and that fainting constitutes a generalized reaction to fear of injury, whether real as in the first group, threatened as in the second, or imagined as in the third.

If we now go back to the wider field of biology we find that Charles Darwin, writing in 1872 on the effects of emotion in animals noted a singular paradox. He described the reaction to terror, the trembling, sweating, rapid breathing and tachycardia, and felt that this reaction indicated a preparation on the part of the body for defense. But he also noted certain contradictory manifestations—loss of muscle strength, loss of sphincter tone, prostration and actual fainting.

Walter Cannon's classical work on the physiological concomitants of emotional states has substantiated and expanded Darwin's observations. He demonstrated experimentally that under conditions of terror the organism was prepared for intense physical effort by basic primitive neuro-muscular and neuro-vascular reflexes. But he, too, recognized contradictory manifestations, and showed that an emotion such as terror may not only stimulate, but may also inhibit and depress. Thus an animal may be paralyzed with fear. Engel and Romano feel that it is this biological contradiction that supplies the key to the understanding of common vasodepressor syncope.

We should now be able to take all the premonitory signs of common fainting and fit them neatly into two groups, those due to stimulation and those due to inhibition. But we are at once defeated in such an attempt because homeostatic reflexes provide immediate compensatory reactions. Thus are we to consider pallor a purposeful reaction to prevent bleeding from wounds, or an effort to compensate for undue vasodilation? In general, however, we can consider that stimulation provokes the tachycardia, sweating, increased blood supply to muscles and increased respiratory rate, whereas inhibition provokes the diminished muscle tone and strength, the sudden drop in pulse, and the immobility which contributes to the fall in blood pressure.

We have talked a good deal about the biological response to terror. People who faint usually experience only mild anxiety, rather than fear or actual terror. What has become of the terror, and why do relatively innocuous situations call forth in the human a biological response to terror?

Psychoanalytical investigation of normal people has shown the existence of a very extensive unconscious mind, harboring all sorts of strong emotional

feelings, including fears of a fantastic nature. Such fears are left over from infancy and childhood, but they are in no way diminished by the passage of years. This is in striking contrast to the consciously remembered fears of childhood, which tend to diminish as we grow older and come to understand our environment better. If you will let me substitute shoes for fears, it is as though we carried with us throughout our lives, in a special compartment under lock and key, all the outgrown shoes of childhood. The weight of such a load would constantly affect our movements in any direction. This normal load of unconscious fears may be greatly accentuated in some people, and through association may become capable of being stimulated by relatively harmless situations. The individual is not aware of these unconscious terrors, but his autonomic nervous system is, and it responds just as though the terrifying situation existed in actuality rather than in fantasy.

In the case of the first time fainter the novel situation is enough to mobilize the unconscious fear of injury. Subsequent familiarity minimizes the anxiety and the surge of primitive fear no longer occurs. In the neurotic repetitive fainter, however, the underlying fear of injury is so intense that the same procedure, such as venipuncture, will provoke the reaction over and over again.

We have now seen the animal responding to terror with physiological preparations for fight or flight, and we have uncovered the missing terror in these situations in which the human shows a similar physiological response. But why is this purposeful physiological reaction annulled by inhibitory mechanisms?

A perception of the impossibility of escape seems to be a factor. In the human several more or less conscious feelings combine to make escape appear impossible. Consider our subjects. Characteristically, they are men, often big strapping ones, and they are all of course very brave. This fact, plus their reason, plus long years of social training, defeats any such absurdity as fleeing from or fighting a technician with a syringe. Thus a situation is encountered which, by association and due to unconscious sensitization, results in extreme unconscious fear of injury, together with the physiological concomitants of such fear. Appropriate action is unthinkable, and escape therefore impossible. Let me remind you again that if action in the form of exercise is taken the changes tend to be reversed.

But the question has been answered only partially. Awareness of the impossibility of escape might contraindicate effort, but why should it produce actual inhibition? A reaction so crippling to the mechanisms of defense is in striking contrast to the amazing devices developed by nature for self-preservation. At least an attempt to escape would seem more purposeful. In conclusion one can only guess that the victim, apparently unable to escape, and overwhelmed by fear, finds it preferable to lose consciousness rather than to continue to perceive the danger.



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# THE ASSOCIATION OF CAPILLARY SCLEROSIS WITH ARTERIOSCLEROSIS AND PHLEBOSCLEROSIS; ITS PATHOGENESIS AND CLINICAL SIGNIFICANCE \*

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THIS contribution represents a study of the lesions of the capillaries in organs in which either the main arterial trunk or veins reveal sclerosis. In the lung, pancreas and kidney the vascular lesions show arteriosclerosis; in the liver and spleen, phleboscrosis. In the former, the capillary lesions are affected by forward intravascular pressures, in the latter by backward pressures. In previous publications <sup>1, 2, 3</sup> I tried to show that prolonged normal intravascular pressure is the dominant conditioning factor in the production of arteriosclerosis and phleboscrosis and that these lesions come earlier and are intensified under the influence of its increased gradient, hypertension. Likewise the capillary lesions which we term "capillary sclerosis," are most prominent in conditions in which prolonged arterial or venous hypertension exists. Capillary sclerosis bears so many of the morbid anatomical attributes of arteriosclerosis or phleboscrosis that it represents a veritable vascular sclerosis "en miniature." Indeed the almost constant association of capillary sclerosis with sclerosis of the larger vascular trunks within an organ enables one to predict that when arteriosclerosis or phleboscrosis is present, the capillaries will show sclerosis and vice versa. For the combined lesions, the term arterio- or venocapillary sclerosis appears applicable. Although the capillary lesions of many of the parenchymatous organs have been described repeatedly, observations are singularly silent on their significance, their relation to sclerosis of the tributary vascular trunks and to pressure changes. The capillary changes of the following organs subject to intravascular hypertension will now be described: (1) lungs; (2) pancreas; (3) kidneys; (4) liver; (5) spleen.

1. *Lungs.* Normally the capillaries of the uninjected and collapsed lung are hardly visible and one may recognize them only as occasional narrow slits in the wall of the alveoli slightly larger than the contained erythrocyte. The wall of the alveolus is narrow, uniform in thickness, and, with the exception of a bulge of the lining epithelium the alveolar lining is smooth. The wall of the alveolus consists of an alveolar basement membrane and a capillary basement membrane and between the two a sparse fibrillary connective tissue network with an occasional mesenchymal cell. The only anastomotic channels between the pulmonary and greater circulation are capillaries communicating between the alveolar capillaries and the capillary bed of the bronchial arteries, so that the circulation within the lung is practically a closed one.<sup>26</sup> I have

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found sclerosis of the pulmonary capillaries only when gross arteriosclerosis of the pulmonary vessels is observed. In previous papers<sup>2, 3</sup> I have tried to show that gross arteriosclerosis of the pulmonary vessels only occurs under conditions in which a hypertension of the pulmonary circulation can be predicated. These are in the order of frequency, mitral disease and especially mitral stenosis, prolonged congestive failure, emphysema, extensive pleural adhesions, marked diminution in lung volume from whatever cause, certain cases of marked scoliosis, open ductus Botalli and communications between the right and left heart (but only when the shunt is from left to right). I have not observed arteriosclerosis of the pulmonary vessels under any other conditions. The independence in incidence between gross arteriosclerosis of the greater and pulmonary circulation, and the invariable sequential relationship of sclerosis of the pulmonary artery to hypertension of the lesser circulation affords to our view the strongest support for our contention that the largest conditioning factor in the production of arteriosclerosis is intravascular tension. The independence in the incidence of arteriosclerosis in the two systems is in all probability due to the fact that the pressure in the pulmonary artery is only one sixth that in the aorta. It is significant that, even though a hypertension of the pulmonary circulation never approaches that of the normal intrabrachial pressure an arteriosclerosis of the pulmonary artery may arise. It is well to consider that it is not the height of the pressure, but rather the duration that determines the presence or absence of the arteriosclerosis. This becomes manifest in correlating clinical data with the anatomical findings.

In the earliest phases of capillary sclerosis, the alveolar wall appears beaded. The capillaries are distinctly dilated and the basement capillary membrane is thickened (figure 1). In cross section, the capillaries bulge into the alveolar space. In more advanced phases the dilatation of the capillaries and the thickening of the capillary basement membrane become more pronounced so that the alveolar wall becomes much thicker than normal and the beaded appearance becomes more pronounced. The capillaries now contain as many as five or six erythrocytes instead of one (figure 2). In this stage, one notes a profound increase in the connective tissue content of the alveolar wall, this increase consisting almost entirely of the extensive thickening of the capillary walls. In a later stage, the connective tissue content of the alveolar wall becomes excessive (figure 3). The connective tissue is cellular, the walls of the alveoli become much thickened and there is a corresponding narrowing of the alveolar spaces, accounting in a large measure for the diminution in vital capacity in cardiac disorders. In many areas hyalinization of the capillary basement membrane is apparent. The capillaries in this stage have become to a large extent obliterated. In the terminal stage the connective tissue transformation of the alveolar wall is so great that the alveolar space becomes but a narrow chink, and the lining epithelium becomes cylindrical in appearance, as in the embryonal lung (figure 3). Capillaries are almost entirely absent, the only vessels persisting in these areas

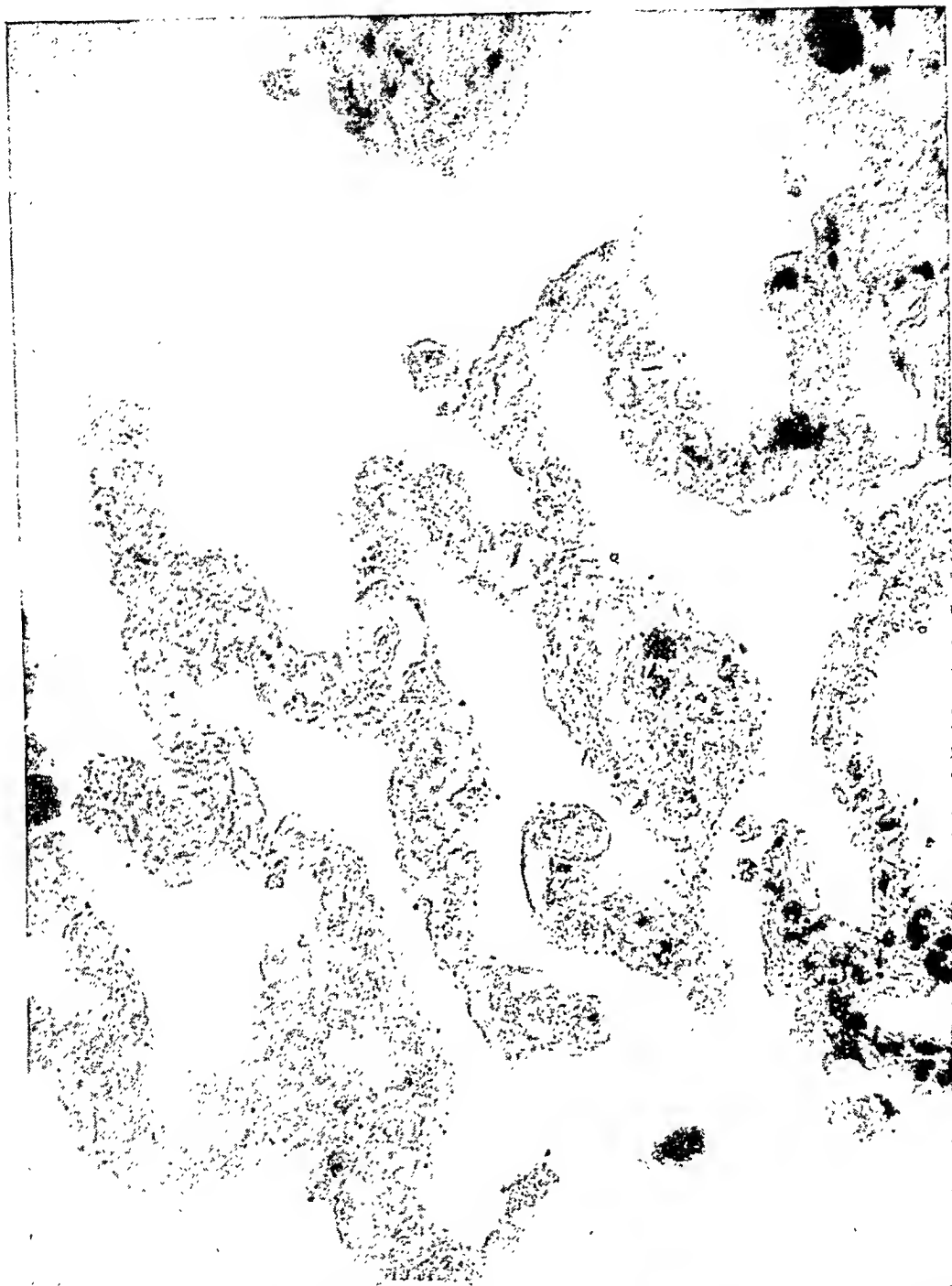


FIG. 1. Early phase of capillary sclerosis. Lung from case of mitral stenosis, showing beaded appearance of alveolar wall due to dilatation and thickening of capillary walls.

being the greatly sclerosed arterioles and arteries. These changes are commonly seen in lungs that have been infarcted, but infarction is only a lesser factor in the production of an increase in connective tissue. One can note in the immediate vicinity of such areas profoundly sclerotic arterioles with the lumen almost obliterated by internal thickening. Undoubtedly, therefore,

diminution in blood supply is in a large measure responsible for the increase in connective tissue.

These marked changes have been confirmed by von Jeddelloh <sup>4</sup> and Parker and Weiss. <sup>5</sup> Parker and Weiss describe in addition changes in the arterioles similar to those described in the kidney in malignant hypertension.

The dilatation, the thickening of the walls, the hyaline changes and the connective tissue proliferation represent morbid changes which are part and parcel of true arteriosclerosis, and which I believe can be viewed as the result of a mechanism identical with that which is responsible for the development of arteriosclerosis. Obviously reduplicating of the elastica cannot occur, since the elastic layer is wanting in capillaries. We have tried to show that atheroma, calcification and mucoid degeneration are only secondary or facul-

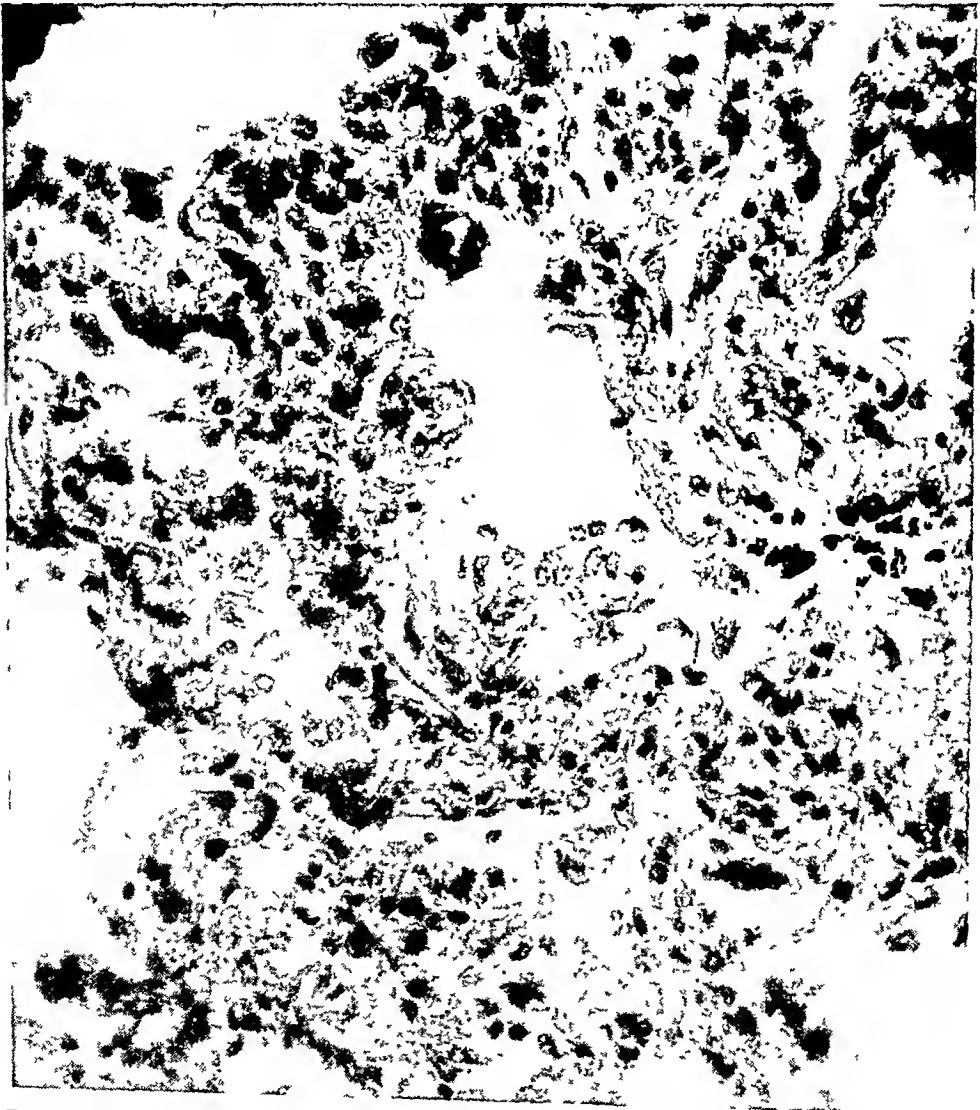


FIG. 2. Later phase of capillary sclerosis. Lung from case of mitral stenosis showing greater thickening of alveolar wall. Walls of individual capillaries greatly thickened and some are hyalinized. Note capillary bulging within the lumen of the alveolus in the center.



FIG. 3. Terminal phase of capillary sclerosis. Lung from case of mitral stenosis. Note intense sclerosis of alveolar walls with almost complete obliteration of the capillary bed. Also note reversion of the morphology of the lung to the embryonal type.

tative lesions in arteriosclerosis. <sup>6</sup> In other words, the changes in the capillaries of the lung in hypertension of the pulmonary circulation represent an extension of the vascular sclerosis of the grosser arteries of the lungs.

That these lesions when found in mitral stenosis are not the result of rheumatic fever is shown by the identity of the capillary lesions in hyper-

tension of the pulmonary circuit due to other causes, congenital cardiac lesions, for instance.

Teleologically one may deem the capillary sclerosis as a compensatory mechanism, at least in its earlier stages. The widening of the capillaries permits a greater flow of blood to counteract the decreased rate of capillary flow consequent upon the increase of peripheral resistance, thus permitting a wider surface for the diffusion of oxygen. The thickening of the capillary wall is compensatory to the increase in intracapillary pressure, thus obviating possible rupture of the delicate basement membrane. Both these compensatory mechanisms accord with the laws of Thoma on the growth of blood vessels.<sup>7</sup> In the later stages these morbid processes overshoot the mark, and bring in their train consequences that lead to decompensation. We refer particularly (1) to the progressive diminution in the calibre of the alveolus which results in diminution in vital capacity; (2) to the progressive thickening which interferes with the exchange of oxygen; (3) to the obliteration of the capillary bed which increases the peripheral resistance and (4) to the sclerosis of the arterioles which may lead to thrombosis or rupture.

2. *Pancreas.* The capillary sclerosis is seen in the islands of Langerhans. These are glomerular-like structures consisting of a network of capillaries between which are the secreting cells. The diameter of the capillaries is somewhat wider than the interacinar capillaries.<sup>8</sup> The capillaries have a thin basement membrane and a delicate endothelial lining similar in structure to the hepatic sinusoids but without Kupffer cells. The islands are richly supplied with blood which sometimes comes from an efferent arteriole or from the neighboring interacinar capillaries. There is a rich anastomosis between the capillaries of the islands and those of the interacinar rete.<sup>9</sup>

Capillary sclerosis of the pancreas is best studied in diabetes mellitus. Opie,<sup>10</sup> in his classical monograph, describes hyaline deposits of the capillary wall, which according to Warren<sup>11</sup> are due to the production of intercellular substance by fibroblasts and possibly by the endothelial cells. The hyalin is not always uniform in distribution, but occurs as scattered groups of irregular rounded globular masses, with compressed island cells between. Often the island is completely hyalinized (figure 4). Opie also found that hyaline degeneration of the islands is often accompanied by interacinar fibrosis of varying degrees, and nearly always with arteriosclerosis of the grosser vessels of the pancreas.

Cecil<sup>12</sup> found lesions of the islands in 88 per cent of diabetics. As a rule, the majority of islands are affected. In accord with Opie, Cecil found that the hyalin is deposited along the walls of the capillaries of the islands. Cecil also describes fibrous sclerosis of the capillaries (figure 5). In these islands, the fibrous wall of the capillaries is definitely increased in thickness, converting the vessels into coarse septa which extend in from the capsule. Of 76 cases of diabetes mellitus, 42 showed sclerosis of the capillaries, while 27 showed hyaline changes. In many capillaries both hyaline degeneration and

sclerosis were associated. Cecil found arteriosclerosis of the main vessels of the pancreas, in all but seven of 86 cases of diabetes mellitus.

Warren's <sup>11</sup> description of the changes in the islands of Langerhans follows Opie's and Cecil's closely. He found hyalinization in 96.6 per cent of diabetics over 40 years of age. He found fibrosis less frequently than Cecil,

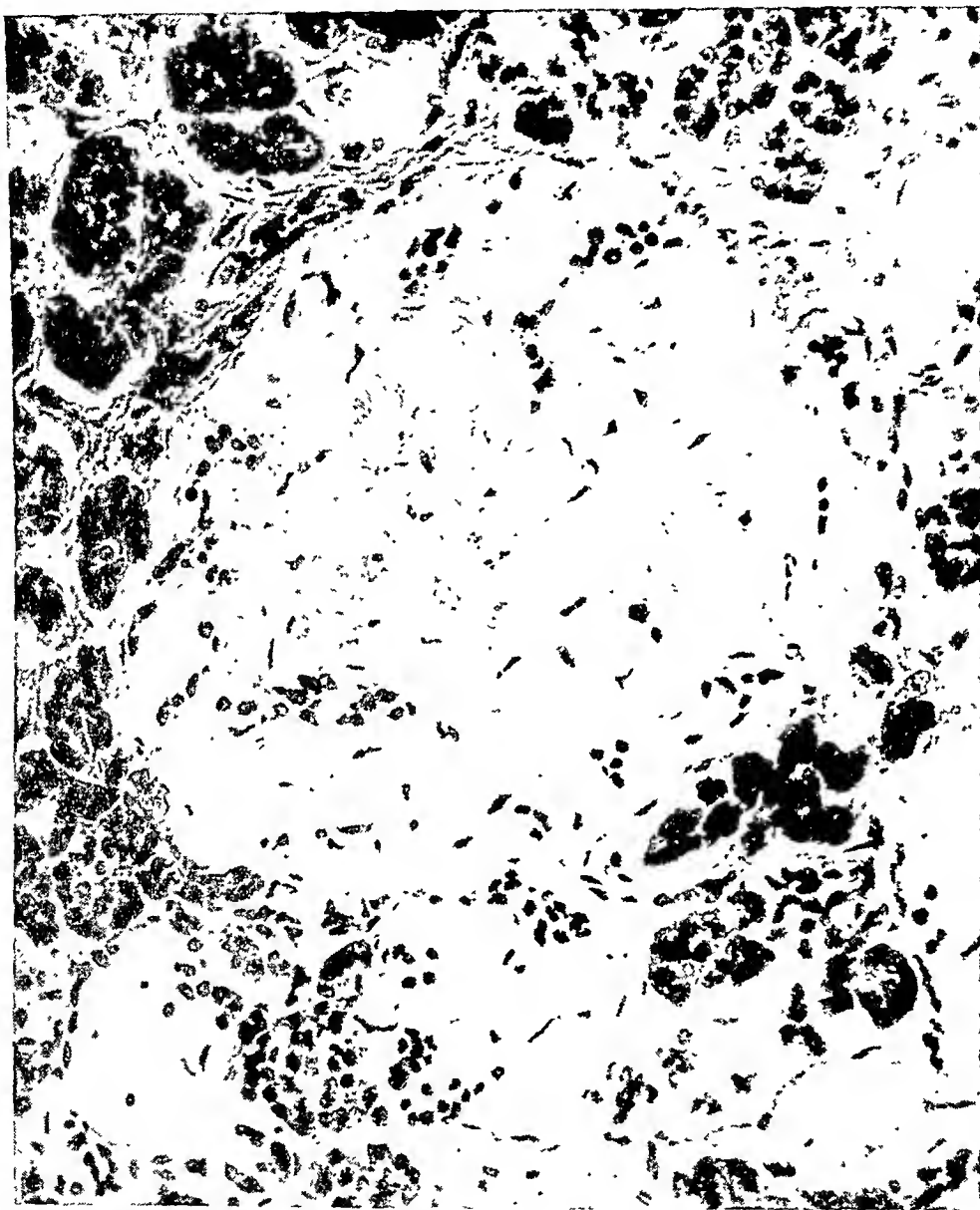


FIG. 4. Island of Langerhans showing complete hyalinization of capillary walls.

in 27 per cent. Hyalin deposits and sclerosis occasionally occur in different islands or even along the same vessel. Fibrosis also tends to occur in older individuals, although of the lesions found in young people, it is one of the more frequent. He finds that arteriosclerosis of the pancreatic vessels is always accompanied by interacinar and interlobular fibrosis. That island



lesions are not a specific property of diabetes is shown by his finding of 2 per cent hyalin and 7.5 per cent fibrosed islands in the pancreas of non-diabetics. When the process becomes sufficiently marked to destroy the secreting cells of the islands, diabetes will develop.

The vascular pattern in the pancreas, namely capillary sclerosis associated practically always with arteriosclerosis, is precisely what we have described

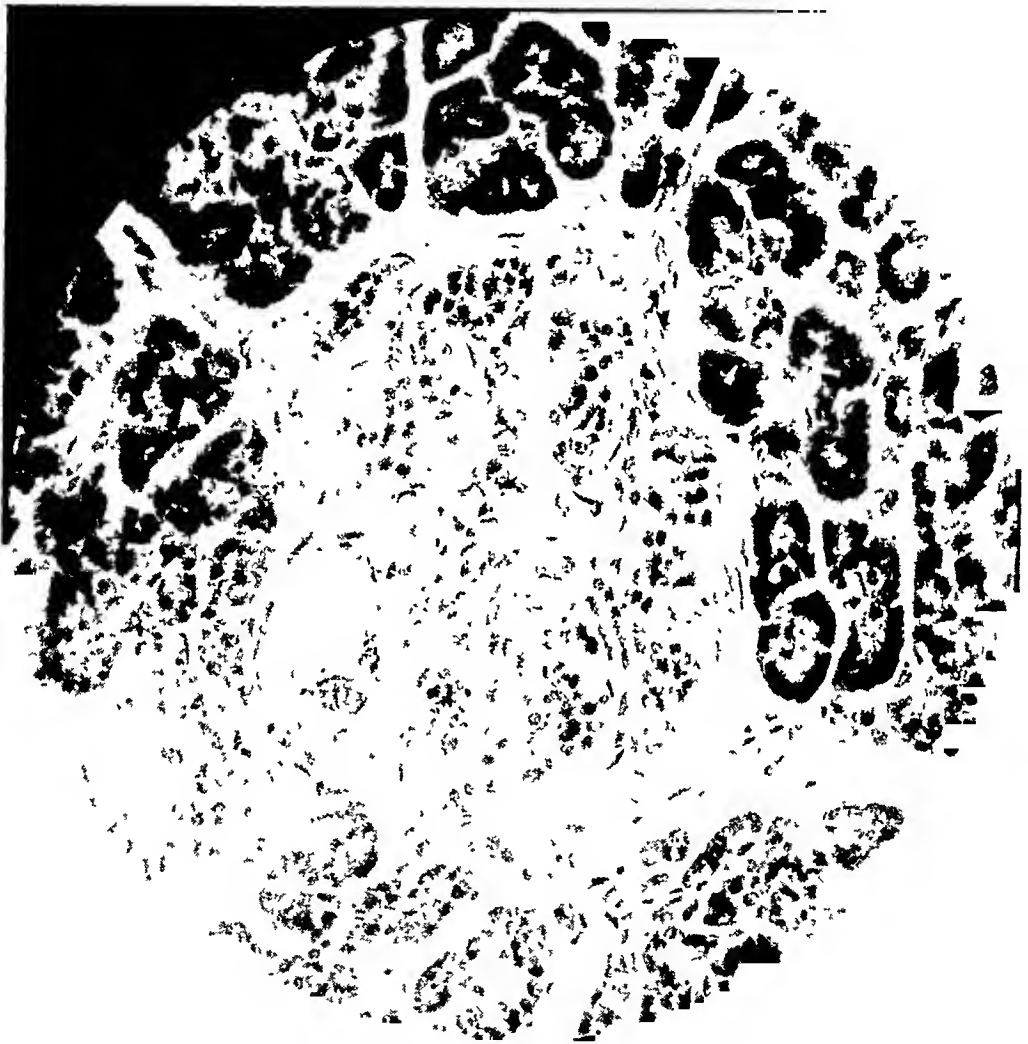


FIG. 5. Island of Langerhans showing fibrosis of capillary walls. (From Joslin, Root, White and Marble, *Treatment of Diabetes Mellitus*, 1940, Lea and Febiger, Philadelphia.)

in the lung. The genesis of the lesion, however, cannot always be ascribed to hypertension of the greater circulation, since hypertension is present in diabetes in only 52 per cent according to Joslin<sup>13</sup> and 39 per cent according to Kramer.<sup>14</sup> The probable reason why diabetes is not more common in hypertension is because the capillary circulation in the islands possesses a comparatively wide shunt to the interacinar capillaries thus minimizing the insular intracapillary pressures. The capillary circulation is not therefore as closed as in the lung. It might be argued that the arteriosclerosis is the

droplet degeneration to complete necrosis, endothelial proliferation, adhesion of the capillary tufts and occasionally, leukocytic accumulation. These changes are usually associated with necrosis of the afferent arteriole and may occur not only in essential hypertension but also in chronic glomerulo-nephritis. There appears to be a fairly consistent relation between arteriolar necrosis and prolonged excessive diastolic pressures.

In my experience, capillary sclerosis of the glomerulus is practically always associated with arteriosclerosis of the renal vessels. Why the brunt of the hypertension is thrust on the renal arterial vasculature rather than on the remaining portions of the arterial tree of the greater circulation is a problem that still awaits solution.

As in the lung and liver the early dilatation of the glomerular capillaries and thickening of the basement membrane may be viewed as compensatory to the hypertension. In the later stages the severe sclerosis undoubtedly contributes to a progressive renal insufficiency, depending on the intensity and extent of the sclerosis. Nevertheless, it is difficult to appraise the functional consequences for a number of reasons. First: the compensatory mechanisms. The thickened capillary walls will reduce the filtration rate so that certain substances, especially the phosphates, sulfates and the nitrogenous products of metabolism will be retained; but the acidosis and the azotemia are offset by the diminution of water absorption by the tubules, permitting a greater water excretion, and a lowering of the specific gravity of the urine. When this attains 1010 which is that of the glomerular filtrate, the tubules can no longer compensate by this mechanism and these substances begin to accumulate in the blood. Second: the extra renal factors, especially cardiac. The frequency of cardiac manifestations in hypertensive disease, whether essential or associated with glomerulo-nephritis, need not be emphasized. That these affect glomerular functions is evidenced by the proteinuria and occasional azotemia which arise in cardiac failure. Furthermore, a reduction in blood pressure, from a coronary thrombosis for instance, will cause an oliguria or anuria and again an azotemia. In the terminal phases, especially when the capillary sclerosis is excessive and is associated with necrosis, proteinuria and hematuria are the rule.

4. *Liver.* The hepatic sinusoids possess a delicate basement membrane lined by a sparse endothelial layer and the Kupffer cells which have an independent function.<sup>46</sup> The sinusoids are occupied by blood which arises from the terminal branches of the hepatic artery and the portal vein which course through the interlobular spaces. According to Wakim and Mann<sup>25</sup> there are arteriovenous connections between these two terminal branches. The sinusoids drain into the central veins and thence into the hepatic veins.

In a previous publication<sup>24</sup> I tried to show that capillary sclerosis around the central veins of the hepatic lobule was invariably associated with dilatation and phlebosclerosis of the hepatic veins and that the summation of this process represented the conventional type of cardiac cirrhosis. Phlebosclerosis of the hepatic veins is an exquisite example of the causal relation of pro-

longed venous pressure to the production of phleboscrosis, since it is found only in conditions associated with sustained hypertension of the hepatic circulation, notably in tricuspid disease and in constrictive pericarditis. The dynamics of the circulation whereby such a sustained venous hypertension is attained have been previously outlined.<sup>15</sup> While cardiac cirrhosis is associated with dilatation and phleboscrosis of the hepatic veins, the latter lesion may occur unassociated with a cardiac cirrhosis, thus differing from the invariable mutual association of the alveolar capillary sclerosis and sclerosis of the pulmonary artery. We ascribe this to the circumstance that in the liver there is a wide release to the intracapillary pressure due to the communications of the capillaries with the portal radicles while in the lung there is only a slight communication between the capillaries of the lung and the capillaries of the bronchial arteries.<sup>20</sup> This accounts for the infrequency of cardiac cirrhosis as compared to the frequency of the analogous changes within the lung.

The observation that hepatic vein sclerosis bears a definite relation to increased venous pressure furnishes a clue to the pathogenesis of cardiac cirrhosis. Cardiac cirrhosis is conventionally viewed as a replacement fibrosis around the central vein, that is, as a condensation of the reticulum, sequential to the capillary dilatation and atrophy of the adjacent liver trabeculae. That the sclerosis does not represent a mere condensation of the reticulum is shown by the fact that the reticulum fibers are both hypertrophied and increased.<sup>27, 28, 29</sup> We believe that the sequence of events is precisely comparable to the capillary sclerosis that we have described in the lung. In the earliest phase there is dilatation of the central vein and the sinusoids in the central portions of the lobule. The trabeculae are correspondingly narrowed. In the midphase one notes a thickening of the connective tissue wall of the sinusoids in these areas, most marked in the sinusoids immediately around the central veins and becoming less and less toward the periphery of the lobule (figure 7). This represents the conventional lesion of passive congestion. The dilatation of the sinusoids may be so excessive that the trabeculae become exceedingly thin. In the latest stage, the central vein and adjacent tributary capillaries become completely obliterated by fibroblasts. To what extent the fibrosis around the central veins represents a replacement phenomenon is difficult to determine. In very advanced instances one may even note occasional hyalinization of the thickened walls of the sinusoids. In passing, one notes frequently in advanced cases, compensatory hyperplasia of the liver trabeculae around the intact portal spaces.\*

We again observe the remarkable parallelism both morphologically and pathogenetically between the morbid process in the lung and in the liver, and to our view, the process in the liver may only be ascribed to the increased capillary pressure. Under normal circumstances the pressure in the inferior

\* We have observed a comparatively high incidence of periportal sclerosis associated with cardiac cirrhosis. Katzin, Waller and Blumgart<sup>30</sup> found such a sclerosis in 23 per cent of patients dying in congestive failure.

vena cava is negative and the probability is strong that the pressure within the hepatic veins is also negative or close to zero. To what elevation the pressure in these vessels attains under the abnormal conditions associated with a hypertension of the pulmonary circuit it is impossible to say. But

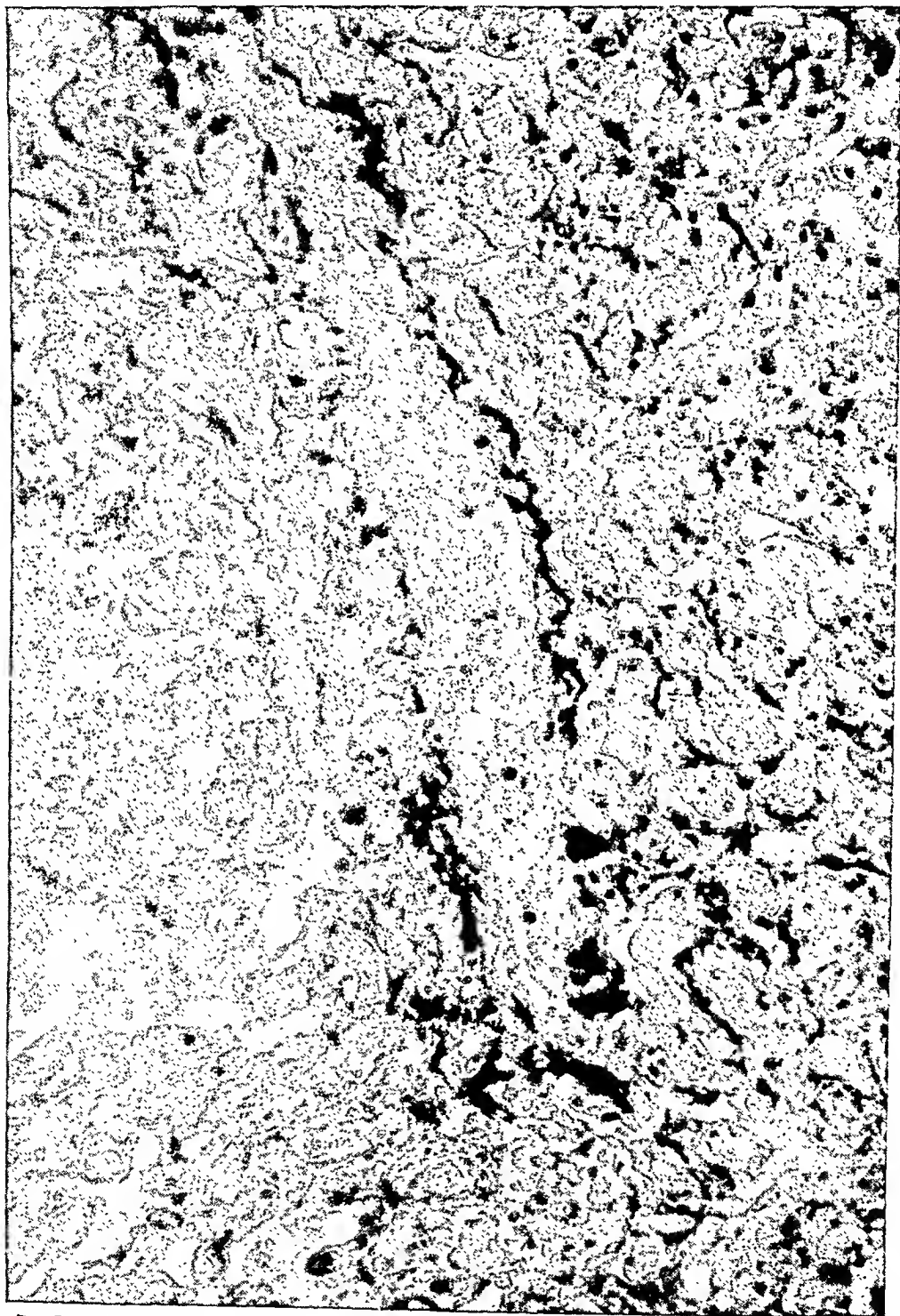


FIG. 7. Liver from cardiac cirrhosis showing sclerosis of capillary walls around central vein.

there is no doubt that the dilatation of the hepatic veins and their tributaries is an important element in compensating for the increased pressure within the right cardiac chambers, thus acting as a reservoir. Inasmuch as the pressure in the cubital veins is more or less proportional to the pressure within the right heart, this test should serve as an approximate indication of the pressure within the hepatic veins. During attacks of congestive failure the rise is transient and does not lead to phlebosclerosis of the hepatic veins. In tricuspid disease and especially in constrictive pericardium, the venous pressures are notoriously persistent. The site where the sinusoidal capillary flow meets its first resistance is at its entrance into the central vein and it is precisely here that the fibrosis begins.

The earliest dilatation of the sinusoids, concomitant with the dilatation of hepatic veins, may be viewed as compensatory to the increased resistance encountered by the flow of blood in the capillaries around the central vein, thus fulfilling one of the functions of the liver, namely, as a blood reservoir. This is observed clinically by the enlargement of the liver during the earlier phases of congestive failure when the venous pressure is elevated and its recession when compensation with reduction of venous pressure is restored. Before fairly extensive fibrosis occurs, the other functions of the liver show hardly any impairment. When fibrosis supervenes, decompensating mechanisms ensue and definite impairment of liver function is observed.

The reservoir function of the liver is diminished. The organ no longer enlarges and recedes during periods of congestive failure and under such circumstances, dependent or general anasarca develops due to the prolonged maintenance of increased pressure in the venous segment of the systemic capillaries. In constrictive pericarditis, where a prolonged venous pressure is usually maintained for years, anasarca is always associated.

An extensive fibrosis leads to hypertension of the portal circuit. This is manifest in the morphological evidences of "congestive splenomegaly." These evidences will be discussed under the next heading. Clinically, the most striking example is exemplified in the pericarditic pseudocirrhosis described by Pick, which we believe is the result of prolonged maintenance of a high portal venous pressure.

Hepatic insufficiency. The liver has a wide safety factor so that very extensive liver damage must occur before evidences of hepatic insufficiency arise. Nevertheless, in congestive failure, hyperbilirubinemia, increased urobilogen in the urine and augmented lactic acid in the blood sometimes are observed.<sup>31</sup> Jolliffe<sup>32</sup> with various tests found impairment of liver function in 15 of 16 patients. With the bromsulfalein test, he found impairment of excretion in 12 of 16 patients; Cantarow<sup>33</sup> in 14 of 42.

5. *Spleen.* The terminal branches of the splenic artery as they penetrate the splenic pulp are extremely narrow and consist of endothelium supported by a few longitudinal fibers and elongated spindle cells. These vessels, although termed capillaries, are wider and the walls are more solidly constructed than the capillaries of other organs. It has been amply demon-

strated that these terminal vessels end in a funnel shaped dilatation, the ampulla of Thoma, the walls of which show stomata. The splenic sinuses, the walls of which represent the beginning of the splenic venous system, unlike the veins, are not lined by a flat vascular endothelium but by narrow cells parallel to the long axis of the vessel, with prominent nuclei that bulge into the lumen. The walls of the splenic sinuses are not continuous but like the ampulla of Thoma are perforated with numerous stomata and it is through these stomata that the free blood cells lying within the meshes of the pulp cords flow into the veins. The sinuses unite to form the pulp veins which enter the trabecular veins. The manner whereby the blood flows between the ampulla of Thoma and the splenic sinuses has given rise to controversy as to whether the circulation in the spleen is an open or a closed one. The weight of modern observation is overwhelmingly in favor of an open circulation.<sup>34, 35, 36, 37</sup> The evidences of an open circulation derived from the observation and interpretation of histologic preparations have been convincingly confirmed in the living animal with the aid of the quartz rod illumination technic by MacKenzie, Whipple and Wintersteiner.<sup>38</sup> According to their observations, the blood from the ampulla of Thoma flows directly into the meshes of the pulp reticulum comprising the pulp or Billroth cords which lie between the sinuses. According to MacKenzie and his co-workers, the pulp spaces in the relaxed spleen measure 6 m. in width but the diameter of dilated ones is 16 m. This potential dilatation together with that of the sinuses affords a measure of the distensibility of the normal spleen and accords with the observation of MacMichael<sup>39</sup> who found that the spleen can be distended to about three times its normal size. The blood then flows from the pulp spaces into the sinuses through the stomata and thence to the trabecular veins which unite at the hilus to form the splenic vein. The pulp spaces are the only means of communication between the arteries and veins within the spleen and represent therefore the analogues of the capillaries in other organs that have a closed circulation.

In a recent study<sup>40</sup> of the pathogenesis of "congestive splenomegaly" in 86 cases in which a cause for a hypertension of the portal circulation was demonstrable (all but two were autopsy cases) I was able to show that the splenomegaly was the result of a progressive veno-capillary sclerosis. The finer morphology of these spleens was studied from the biological point of view and the changes were traced from the earliest to the most mature phase. In this we were aided by the simultaneous study of an accessory spleen in a few cases. The evolution is identical no matter what the cause of the portal hypertension may be. The earliest stage is seen in fresh red thrombosis of the portal or splenic vein. The spleen is large, approaching that of extreme distensibility of the normal organ (450 gm.). The spleen is so distended with blood that the sinuses are not visible. The pulp cords of Billroth are broken up; the pulp cells are normal but widely dispersed. In the succeeding stage when the thrombus has become gray and adherent, the sinuses again become visible but are widely distended and the lining endo-



thelium is flattened. The pulp cords are narrow and the pulp spaces are distended with erythrocytes. The cells of the pulp are not as dispersed and remain normal in appearance (figure 8). The spleen has shrunk somewhat. In the next stage when the thrombus has become partially organized, the pulp

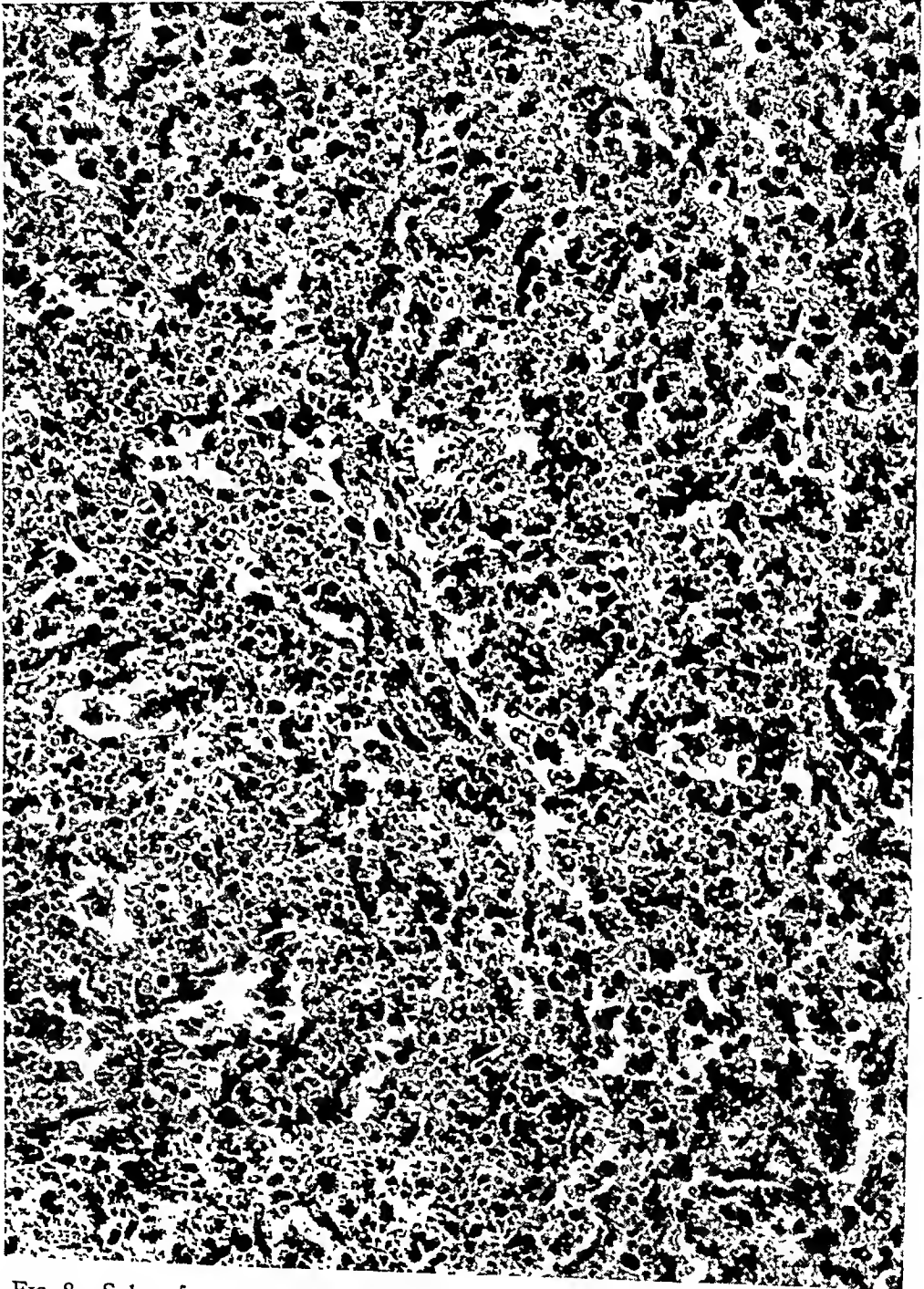


FIG. 8. Spleen from case of organizing thrombus of portal vein showing Billroth cords filled with erythrocytes between which are the sinusoids with flattened endothelium. Earliest phase of "congestive splenomegaly."

cords begin to widen, the pulp cells increase and have undergone a fibroblastic change. The pulp spaces show an appreciable diminution in erythrocyte content. Well defined sinuses appear which are still dilated and the lining endothelium is no longer flat. When the thrombus has become firm and well organized, the pulp cords become still wider and the pulp spaces contain fewer erythrocytes. The pulp cells now show not only a fibroblastic change but they are increased. The sinuses are abundant, less dilated and the fibrillar reticulum around the sinuses is thicker and denser. When the thrombus has become completely fibrous, the pulp cords are wide and the pulp spaces contain only a minimal quantity of blood. The pulp cells become predominantly fibroblastic and the sinuses show extensive hyperplasia (figure 9). The spleen is now much larger than normal. When the thrombus becomes so completely organized as to be termed "cavernous transformation," the maturation of the process almost attains its maximum. The pulp cords become sclerosed and canalized and the pulp spaces contain only a minimal number of erythrocytes. The pulp cells are now all flat fibroblasts. The sinuses are sharply defined and definitely hyperplastic. The lining endothelium is unusually prominent (figure 10). The spleen is now huge, averaging around 1000 gm. The maximum phase was noted in one spleen, the result of cavernous transformation of the splenic vein. Here the pulp cords were completely transformed into firm fibrous connective tissue, so that in many areas the containing pulp spaces appeared bloodless. In this organ the splenic circulation had been converted from an open to a practically closed one (figure 11).

All these stages except the terminal were noted in spleens in hypertension of the portal circulation no matter what the origin. The maladies studied were the following: portal, biliary and toxic cirrhosis; the cirrhosis associated with hemochromatosis and schistosomiasis; acute, subacute and chronic thrombosis of the portal or splenic veins, including cavernous transformation of these veins: cardiac lesions with prolonged failure, with hepatic fibrosis and without: constrictive pericarditis and obstruction of the hepatic veins. The least mature are the acute obstructions of the portal vessels and those in which the portal hypertension is of central or cardiac origin. The latter never achieve a full maturity, in all probability because the hypertension is not sufficiently prolonged, except in constrictive pericarditis. In the latter cases the lesions are correspondingly much more mature. The most advanced lesions occur in chronic extrahepatic vascular obstructions and have been termed "congestive splenomegaly." In between but approaching the latter are the various forms of hepatic cirrhosis and obstruction of the hepatic veins. The morphological differences in all these varieties are quantitative and not qualitative. The largest spleens and the most mature lesions occur in splenic vein obstruction. The proofs that reveal that hypertension of the portal circulation is the dominant factor in the production of these lesions are the following: 1. In portal cirrhosis, in the cirrhosis of schistosomiasis, in the cirrhosis of toxic hepatitis, in chronic thrombosis of the



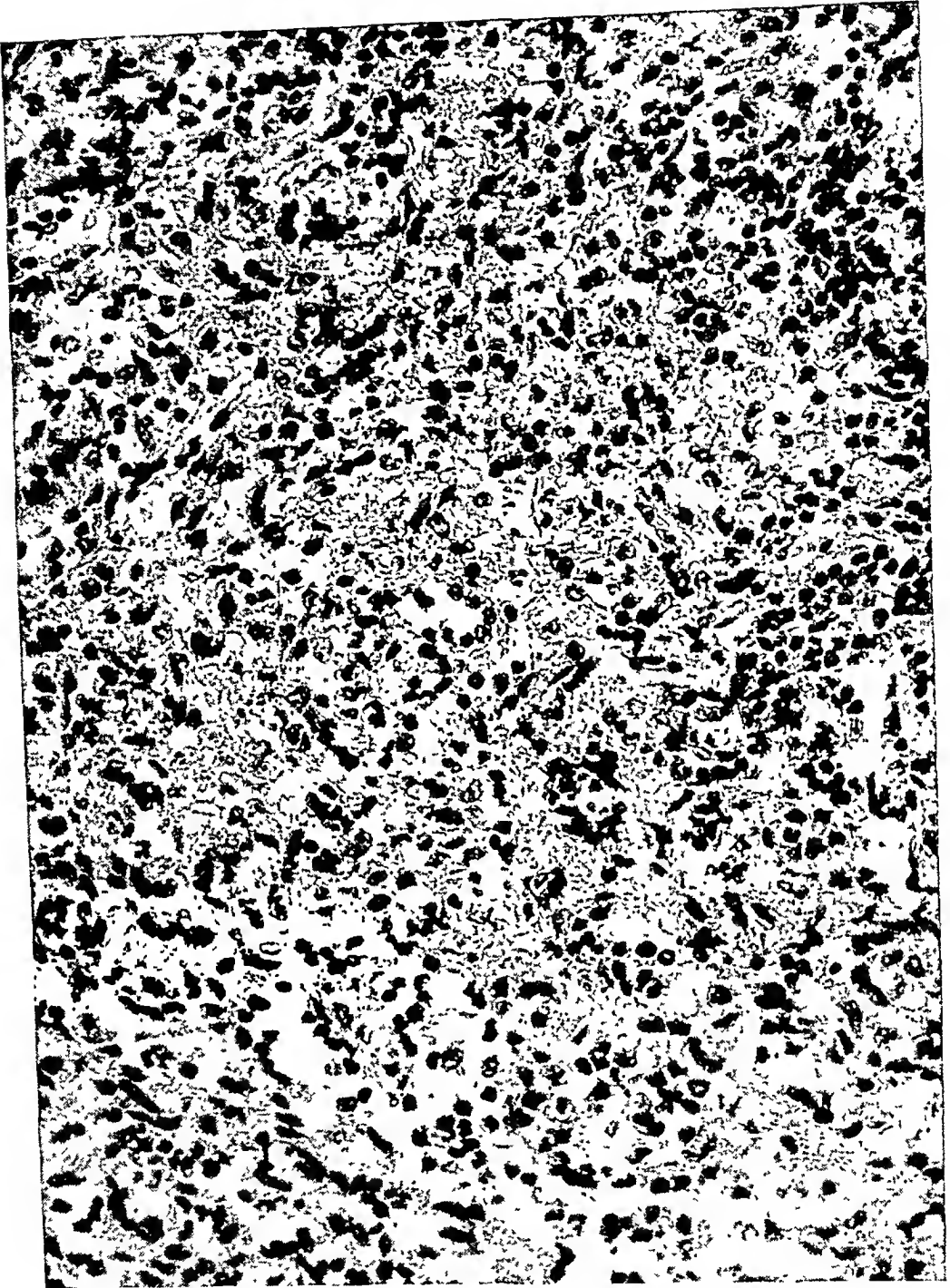


FIG. 9. Spleen from case of constrictive pericardium showing beginning fibrosis and widening of Billroth cords between which are well formed sinusoids with prominent endothelium. Midphase of "congestive splenomegaly."

portal and/or splenic veins Thompson <sup>41</sup> and Rousselot <sup>42</sup> made simultaneous measurements of the pressures within the splenic and antebrachial veins and found the pressure in the splenic vein appreciably greater than in the antebrachial veins, usually about 10 times as high. 2. In constrictive pericarditis, where high venous pressures are consistently maintained, the same changes

occurred in the spleen, although they attained only what may be termed the midphases of the process. 3. In the cases in which an accessory spleen was studied, the lesion was much less advanced than in the main organ. This was undoubtedly due to the much smaller venous tributary, in which the pressure was not quite as elevated as in the main branch. 4. The develop-

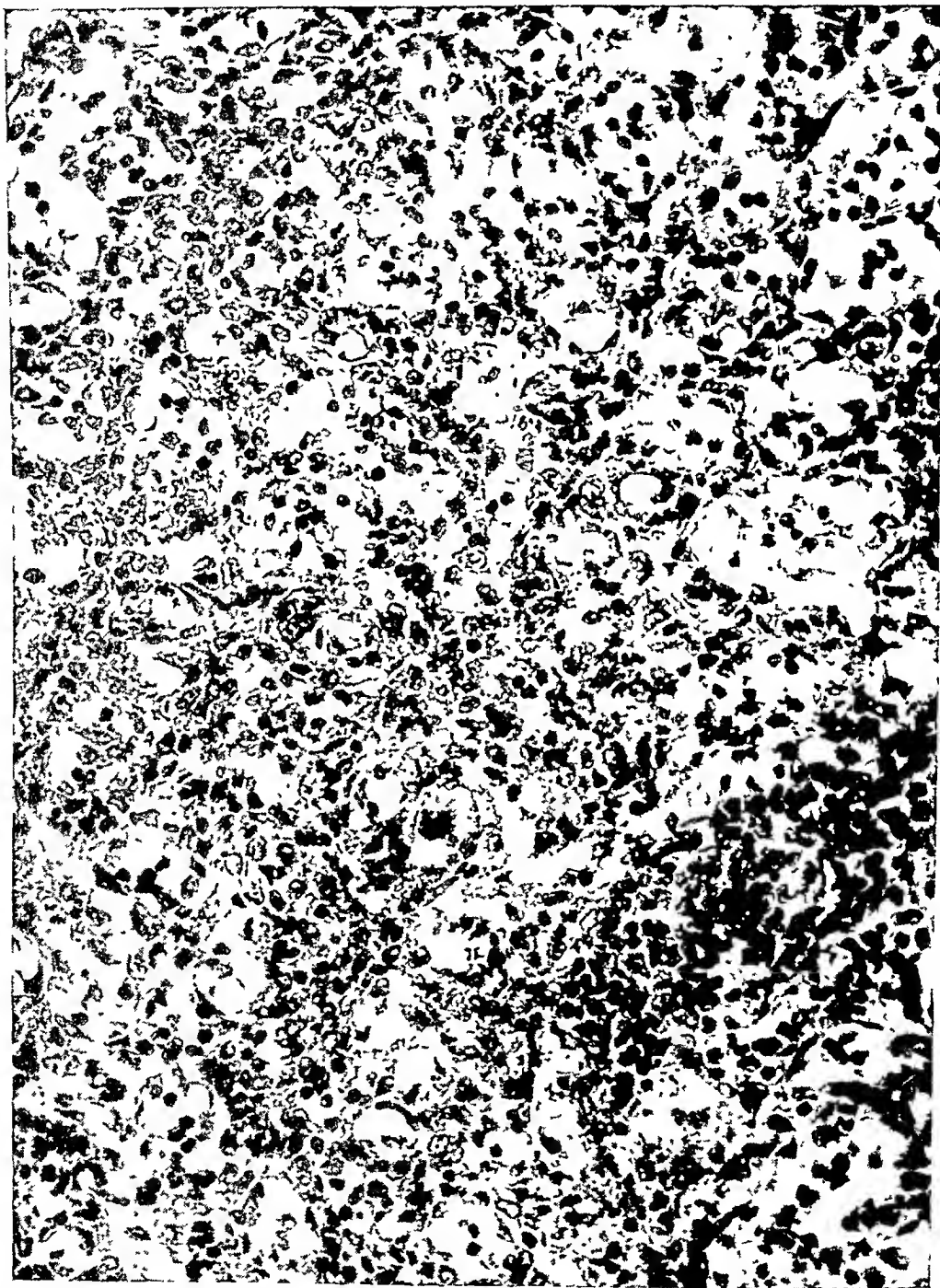


FIG. 10. Spleen from case of cavernous transformation of portal vein showing more advanced fibrosis of Billroth cords and sinus hyperplasia. Late phase of "congestive splenomegaly."

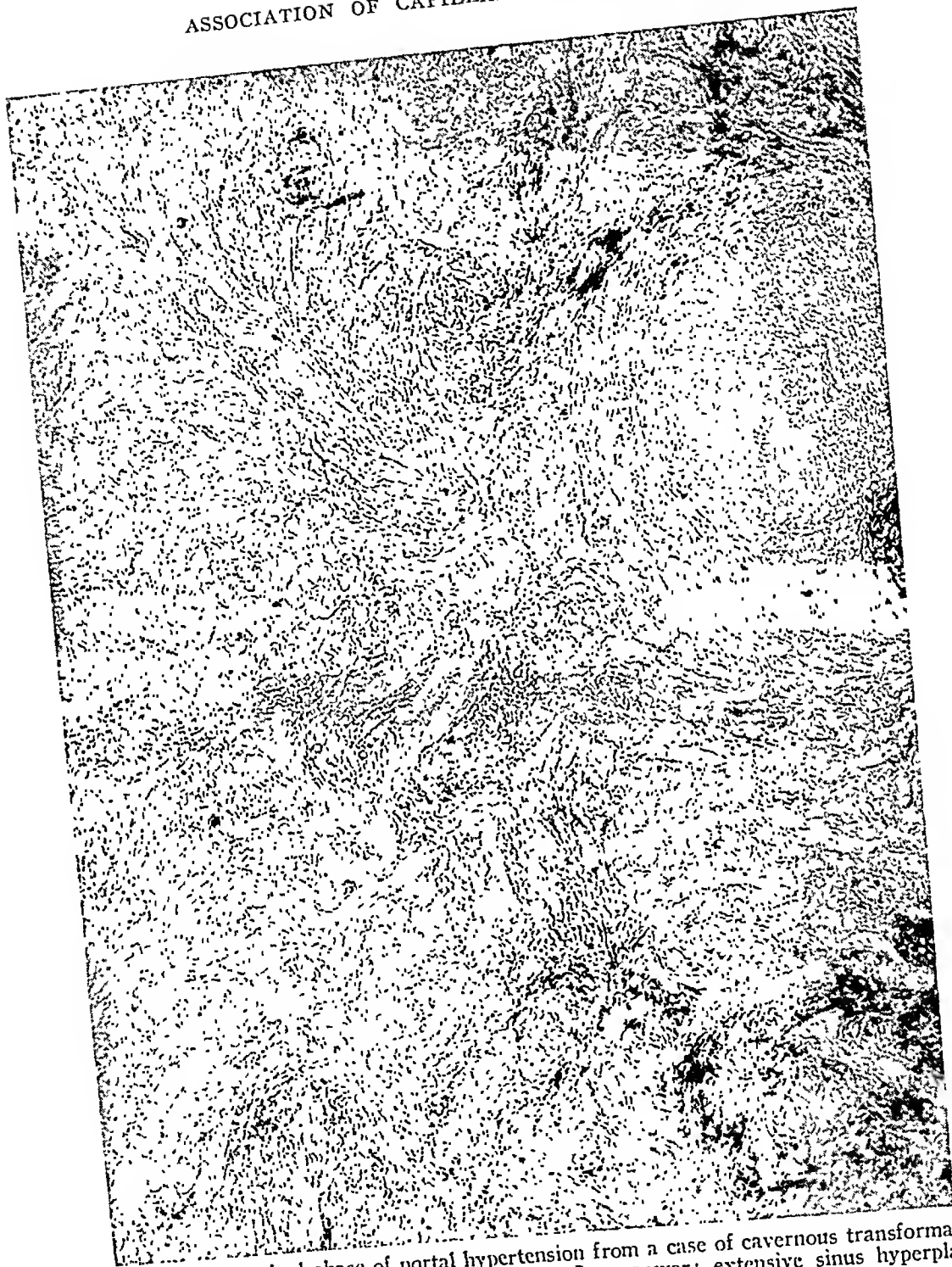


FIG. 11. Terminal phase of portal hypertension from a case of cavernous transformation of the splenic vein. Spleen 24 by 15 by 6 cm. Low power; extensive sinus hyperplasia, mature fibrosis. In this spleen the circulation has been converted from an open into a practically closed one.

ment of a compensatory collateral circulation between the portal and general circulations around the lower end of the esophagus. This occurs only in the intrahepatic and extrahepatic obstructions, but not in the portal hypertension of cardiac origin. In the latter an anastomotic circulation cannot arise be-

cause the venous pressure in the portal and general circulation are presumably equal. A collateral circulation only arises when an area which has been subjected to prolonged venous pressure must divert its blood into an area where normal pressures prevail. 5. The frequent association of phlebosclerosis of the portal vessels. It seems remarkable that the frequency of phlebosclerosis (under the stimulus of venous hypertension) and its morphological similarity to the sclerosis that occurs in arteries was entirely overlooked as a clue to the possibility that portal hypertension was the direct cause of the lesions of "congestive splenomegaly" until MacMichael's study in 1934. But he also held that the same factor that produced the cirrhosis caused the splenic changes. This is hardly tenable in view of the identity of the splenic histomorphology in hepatic cirrhosis and in extrahepatic portal obstruction. The portal veins show thickening of the intima, splitting of the elastica, hypertrophy of the muscular coat and degeneration within the deeper layers with fibrosis. Previously almost every student of hepatic cirrhosis and "Banti's disease" regarded the phlebosclerosis as "primary" and of unknown origin. A number ventured the opinion that it was syphilitic, but without the slightest morphological evidence. The phlebosclerosis is exceedingly common; my own experience is not sufficiently valid to warrant an estimate of the incidence of phlebosclerosis of the portal vessels in hypertension of the portal circulation since the protocols, especially of an earlier date, are silent on this observation; and above all because in the vast majority of instances gross observations and not microscopic study of the veins were reported. Li,<sup>43</sup> however, found that in his cases of hepatic cirrhosis the incidence of phlebosclerosis of the portal or splenic veins was 77 per cent. The probability is therefore strong that a painstaking study of the portal veins in hypertension of the portal circulation would show as high a per cent if not higher.

It is apparent that the peripheral resistance may be anywhere between the heart and the hilus of the spleen. On mechanistic grounds one would presume that, other things being equal, the more distal from the spleen the peripheral resistance, the less the portal hypertension and therefore the less mature the lesions. Such indeed has been found to be the case. But there are other influences that modify the morphological picture profoundly. If the clinical history and the maturity of the splenic lesions are correlated, it was found that, as in pulmonary and hepatic vein sclerosis, the longer the duration of the hypertension of the portal circulation the more mature the lesions. This is also manifest in the marked difference in morphology in acute, subacute and chronic vascular obstructions. Another factor is unquestionably the degree of the portal hypertension. This is indicated by Thompson's<sup>41</sup> observation that the greater the density and distortion of the fibrosis in portal cirrhosis, the greater the splenomegaly. Until systematic studies of portal hypertension at operation are correlated with the maturity of the lesions, no statement can be made concerning the precise effect of the degree of portal hypertension. There is a certain parallelism

between hypertension of the portal and of the greater circulation. In the greater circulation, the most advanced sclerosis of the arteries and of some of the tributary capillaries, notably of the glomeruli, is observed in the "malignant" types in which both systolic and especially diastolic pressures are excessive.

If we view the red pulp spaces in the spleen as the anatomical analogues of the terminal capillaries in organs with a closed circulation, and the very common association of sclerosis of the portal veins, it becomes clear that the later phases of "congestive splenomegaly" represent both in their evolution and morphology a veno-capillary sclerosis, comparable in every way with that we have described in other organs. The progressive sclerosis of the pulp cords of Billroth permits of no other interpretation. The ultimate physiological effects of such a sclerosis will be to convert the circulation within the organ from an open to a more or less closed one and the spleen will lose much of its function as a blood reservoir. What other functions may be compromised awaits future study.

The term "congestive splenomegaly" conventionally adopted at Larabee's<sup>44</sup> suggestion is not strictly accurate, since congestion is not physiologically synonymous with venous hypertension. The term "portal hypertensive splenomegaly" would be more appropriate. The validity of "Banti's disease" characterized by "congestive splenomegaly" has been entirely discredited as a nosological entity, both clinically and anatomically.

#### COMMENT

These five organs in which either arterio- or veno-capillary sclerosis can be demonstrated lend themselves readily to such study because the capillaries can be studied in mass formation, while the tributary arteries and veins are large and the affected capillaries have a more or less closed circulation. Other organs are probably subject to the same influence and such studies we hope to pursue. The probability is strong from the evidences we have submitted that we shall find no or minimal changes in organs that have rich anastomotic outlets for the capillaries. That the systemic capillaries are affected by capillary sclerosis is suggested in the study of the peripheral capillaries in hypertensive disease by the Lombard method, when they are found deformed, tortuous and irregularly thickened.<sup>15</sup>

#### SUMMARY

Capillary sclerosis is an invariable accompaniment of the general sclerotic process that affects the vascular system. When the main artery of an organ is affected by arteriosclerosis, the distal capillaries reveal capillary sclerosis. This has been demonstrated in the lungs, the pancreas and the kidneys. When the main vein of an organ is affected by a phlebosclerosis, the proximal capillaries also show capillary sclerosis. This has been demonstrated in the liver when the hepatic vein reveals sclerosis and in the spleen when the splenic and portal veins show sclerosis. Evidence has been submitted to

show that arterial and venous hypertension within these vessels is the cause of the sclerotic process. In the pancreas and kidney a descrent capillary sclerosis, that is unassociated with hypertension, may occur. We have reason to believe that this is the result of prolonged normal intraarterial tension, since it is associated with the decrescent arteriosclerosis of advanced years. A decrescent venocapillary sclerosis is probably impossible, since venous pressures are low and even under abnormal conditions never approach the normal systemic arterial pressures. We have not observed decrescent capillary sclerosis in the lung for the same reason, since the pressure in the pulmonary artery is only one-sixth that within the aorta.

In the organs affected by arteriosclerosis, the distal capillary sclerosis is the result of forward intravascular pressure; in those with phlebosclerosis, the proximal capillary sclerosis is the result of backward pressure. The capillary sclerosis affects the function of these organs to a greater or lesser extent. Teleologically, the early phases of capillary sclerosis represents a compensatory adaptation to the prolonged arterial and venous hypertension. In the later phases, the decompensating effects of the exaggerated phases of the lesions upon the function of each organ have been outlined.

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# COMPARATIVE STUDIES ON THE IODINE ABSORPTION OF ANAYODIN, CHINIOFON, DIDOQUIN, AND VIOFORM IN MAN \*

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DAVID, Phatak, and Zener, <sup>1</sup> in 1943, published studies made on the toxicity and absorption of Iodochlorhydroxyquinoline (Vioform) and Diiodohydroxyquinoline (Diodoquin) in man. Their studies failed to include Iodoxyquinoline sulphonic acid (Chiniofon) also known as Anayodin or Yatren. Likewise, Diodoquin was not given in its recommended therapeutic dosage; therefore, the blood iodine levels and toxicity were not determined at therapeutic levels. Toxicity studies revealed both Vioform and Diodoquin to be relatively safe drugs since the recommended full therapeutic dosage in the thinnest individual is not over 8 mg. per kg. of Vioform and 30 mg. per kg. of Diodoquin. The lethal dose of Vioform was shown to be 175 mg. per kg. in the guinea pig and 400 mg. per kg. in kittens, and although the lethal dose of Diodoquin could not be determined accurately it apparently occasionally killed guinea pigs or kittens in doses of 50 to 2,000 mg. per kg. but showed its greatest number of deaths at 300 mg. per kg., killing four out of 10 guinea pigs at this level.

The postmortem histologic changes showed liver damage and were similar in type to chloroform poisoning as shown by David, Johnstone, Reed, and Leake <sup>2</sup> in rabbits dying from Vioform. David, Phatak, and Zener <sup>1</sup> believe the toxicity may be dependent more on hyperacidity or intestinal stasis than on the actual amount of the drug administered. Anderson and Reed <sup>3</sup> believe hyperacidity in man can increase the toxicity of Vioform. Anderson, David, and Koch <sup>4</sup> state halogenation of oxyquinoline increased its toxicity in proportion to the atomic weight of the halogen present. David, Phatak, and Zener <sup>1</sup> believe the prolongation of treatment with Diodoquin might increase the danger of absorption and toxicity.

Since direct methods of assay of these drugs are as yet impractical, their absorption after oral administration was studied indirectly by determining blood iodine levels.

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## METHOD

The total iodine in whole blood was determined by the method of Matthews, Curtis, and Brodie,<sup>5</sup> based on the method of Leipert,<sup>6</sup> with modifications suggested by Spector and Hamilton.<sup>7</sup> The procedure involved oxidation of the organic matter, and all iodine to iodine pentoxide by means of chromium trioxide in the presence of sulfuric acid. Phosphorous acid was

TABLE I  
Recovery of Iodine Added to Blood

Iodine Content in 10 c.c. Blood	Iodine Added as KI	Total Iodine Recovered	Iodine Recovered
Iodine in Gammas per 100 c.c.			Per cent
21.4	10	30.0	95.5
16.0	10	24.1	92.6
8.0	50	58.6	101.0
11.2	50	59.7	96.0
13.8	100	108.1	95.0
26.2	100	121.9	97.1
13.6	300	301.1	96.0
15.4	300	308.4	98.1
7.2	500	500.1	98.6
12.0	500	508.9	99.4
4.8	1,000	1,000.8	99.6
17.7	1,000	1,002.4	98.5

used as a reducing agent for the liberation of iodine during the distillation procedure and a potassium carbonate and sodium sulfite solution to trap the iodine as potassium iodide. Oxidation to potassium iodate with potassium permanganate was accomplished by means of the Groak reaction,<sup>8</sup> and titrations were made using sodium thiosulfate with starch indicator. All determinations were run in duplicate.

TABLE II  
Blood Iodine Changes Following Treatment with Vioform  
Daily dosage: 0.75 gm. (=278 mg. iodine)

Patient	Blood Iodine in Gammas per 100 c.c.			
	Before Treatment	3rd Day	7th Day	10th Day
M. D. G.	22	215	360	386
E. C.	8	247	—	241
I. R.	13	147	396	374
J. F. S.	48	419	402	349
J. M.	43	412	525	490
J. G.	8	328	314	298
M. T.	11	365	611	529
A. D.	30	244	500	475
Averages	23	297	444	393

Modifications of the original method were as follows:

1. 10 ml. of whole blood were used for each determination and for oxidation 15 ml. of 10 M chromium trioxide and 75 ml. of concentrated sulfuric acid.

2. Destruction of excess chromium trioxide was accomplished by heating the flask in a hood to a temperature of 200 to 210° C. for five to 10 minutes. Gentle rotation of the flask at intervals during heating served to free the walls of any adherent material. It was found unnecessary to run a stream of compressed air through the flask during this procedure as the contents of the combination digestion distillation flask were small in comparison to its liter capacity and foaming soon ceased after a temperature of 200° C. was reached.

3. Several glass beads with holes were preferred to the antibumps recommended in both the digestion and distillation procedures.

4. Before distillation the contents of the flask were diluted with 125 ml. of double distilled water.

5. During distillation 20 ml. of 10 N phosphorus acid were used for the liberation of iodine.

6. In collection of the distillate 1 ml. of a solution 2 M with respect to potassium carbonate and 0.2 M with respect to sodium sulfite was used.<sup>7</sup>

7. In using the Groak reaction<sup>8</sup> to oxidize potassium iodide to potassium iodate, modifications were those suggested by Spector and Hamilton.<sup>7</sup>

### EXPERIMENTAL WORK AND DISCUSSION

Diodoquin and Vioform have been widely used since the above work was published with no deaths reported from their use and no symptoms of toxicity reported other than occasional slight diarrhea, slight gaseous distention, an occasional sense of abdominal warmth, and occasional anal irritation or pruritus and of a mild degree. Fully 50 per cent of all patients on Vioform and an even larger percentage of patients on Diodoquin register no com-

TABLE III  
Blood Iodine Changes Following Treatment with Chiniofon  
Daily dosage: 36.0 grains (=641 mg. iodine)

Patient	Blood Iodine in Gammas per 100 c.c.			
	Before Treatment	3rd Day	7th Day	10th Day
M. F.	43	69	82	81
R. G.	22	98	69	—
M. J.	10	89	98	84
J. J.	12	37	42	51
I. R.	10	98	106	92
W. S.	3	83	24	21
M. T.	8	118	191	164
Averages	15	85	87	81

plaints. Constipation is sometimes present in Diodoquin, but diarrhea rarely is experienced. Those on Anayodin, Chiniofon or Yatren are more likely to experience diarrhea of moderate degree, but some experience constipation.

TABLE IV  
Blood Iodine Changes Following Treatment with Anayodin  
Daily dosage: 36.0 grains (=641 mg. iodine)

Patient	Blood Iodine in Gammas per 100 c.c.			
	Before Treatment	3rd Day	7th Day	10th Day
E. C.	16	81	100	98
J. G.	7	37	125	97
M. H.	11	60	108	108
A. A. K.	22	127	94	97
J. M.	43	212	152	133
J. S.	8	86	48	102
A. V.	23	112	139	—
M. M.	8	35	49	77
Averages	17	94	102	102

Our studies were all made on ambulatory patients who were receiving the drugs for amebiasis and consisted of 33 tests on Anayodin, 27 on Chiniofon, 49 on Diodoquin, and 31 on Vioform. Since all determinations were done in duplicate to minimize error, this represents a total number of 280 blood iodine determinations. It is recognized that an occasional dose was forgotten by the patient, and in two instances where the levels were low in Diodo-

TABLE V  
Blood Iodine Changes Following Treatment with Diodoquin  
Daily dosage: 28.8 grains (=1,250 mg. iodine)

Patient	Blood Iodine in Gammas per 100 c.c.			
	Before Treatment	3rd Day	7th Day	10th Day
E. A.	9	772	681	681
H. C.	13	1,702	1,798	1,070
J. H.*	8	114	190	137
E. H.	8	529	510	448
S. H.	11	635	677	620
L. R.	17	444	—	444
J. F. S.	13	482	—	592
V. T.	8	455	455	577
A. V.	15	508	—	687
C. W.*	12	107	76	24
R. H.	6	994	1,036	956
J. L.	11	752	922	861
A. M.	17	971	918	899
Averages	12	651	692	615

\* Note Patients "J. H." and "C. W." mistakenly took 3 tablets per day instead of the prescribed 9.

quin it was found the patient had mistakenly taken only three tablets per day instead of the prescribed nine per day. Diarrhea probably was also a factor in causing lower absorption. Blood iodine determinations were routinely done before the drugs were started, again on the third day, on the seventh day, and at the end of the tenth day. Determinations on Diodoquin were

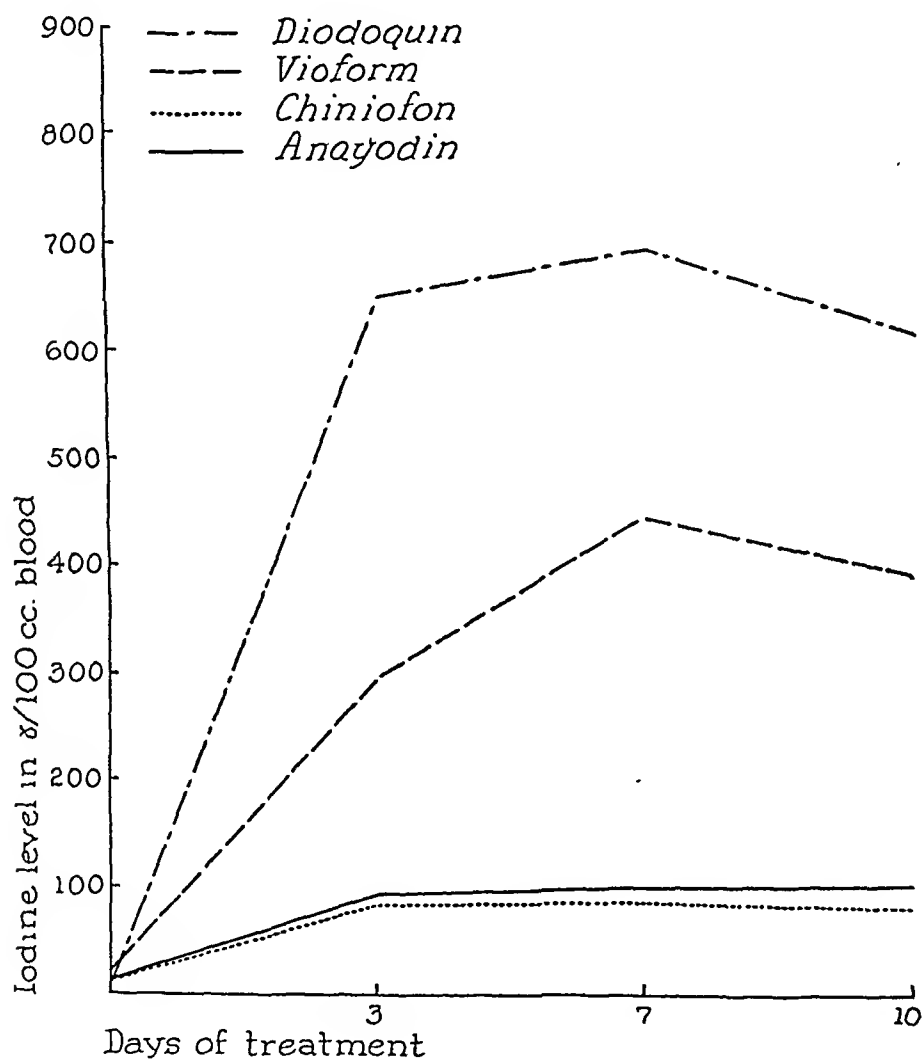


FIG. 1.

also done on the sixteenth and twenty-second days as this drug was routinely given as a course of three weeks but these determinations were not included here since all other drugs are on a 10-day basis. These levels were slightly less than those of the tenth day.

### RESULTS

The blood iodine levels before starting the drugs varied between 3 and 43 gammas per 100 c.c. of blood. The average before Diodoquin was 12, before Chiniofon 15, before Anayodin 17, and before Vioform 23. It is

thought the occasional higher values before Anayodin, Chiniofon, and Vioform occurred because Diodoquin was generally given first, and in some cases one of the other drugs was given after a rest period during which the blood levels had not fallen to normal from the previous medication. No initial value before a course of treatment was found to be higher than 17 gammas except when the patient had finished a previous course of treatment within 10 to 15 days.

Anayodin showed a range on the third day of 35 to 212 gammas, the average being 94; on the seventh day of 48 to 152 gammas, the average being 102; and on the tenth day of 77 to 133 gammas, the average being 102. Chiniofon showed a range on the third day of 37 to 118 gammas, the average being 85; on the seventh day of 24 to 191 with an average of 87 gammas; and on the tenth day of 21 to 164, the average being 81 gammas. Vioform showed a range on the third day of 147 to 419, the average being 297 gammas; on the seventh day, 314 to 611 with the average being 444 gammas; and on the tenth day of 241 to 529 with the average being 393 gammas. Diodoquin showed a range on the third day of 107 to 1702, the average being 651 gammas; on the seventh day of 76 to 1798, the average being 692 gammas; and on the tenth day of 24 to 1070, the average being 615 gammas.

The iodine available in the daily therapeutic dose of nine 250 mg. tablets of Anayodin or Chiniofon containing 27.5 per cent of iodine is 641 mg., that of nine Diodoquin tablets of 210 mg. each with 67 per cent of iodine is 1,250 mg., and that of three 0.25 gm. tablets of Vioform containing 37 per cent of iodine is 278 mg. Thus, it appears that the recommended therapeutic dosage of Diodoquin gives the highest value as measured in iodine, Vioform the next highest value, and Anayodin and Chiniofon the lowest iodine value.

When considered in the terms of absorbability as measured by iodine intake and percentage recovery in the blood, Vioform ranks highest, Diodoquin second, and Anayodin or Chiniofon third.

Absorption apparently was uniform for each drug, a fairly high level being reached on the third day, the highest level on the seventh day, then a slight decline on the tenth day which was maintained or lowered in the case of Diodoquin through to the twenty-second day. The explanation is not evident as no quantitative stool or urine determinations were made. The possible interference with absorption through a slightly irritated mucosal lining should be considered in view of the fact that rectal irritation is sometimes noted. A slightly increased number of movements might likewise be a factor in lessening absorption. These drugs not infrequently have a slight diuretic effect, and although no abnormal urinary findings have been reported one might expect increased excretion to occur. Whether the gastric acidity is a factor in absorption has not been determined. The fact that a reasonable blood level of iodine is attained raises a question as to the effectiveness of these drugs on amebae deep in the walls of the intestine or in other parts of the body. It likewise shows none of them are wholly non-absorbable<sup>9</sup> as stated in the Searle publication on Diodoquin in 1937. A gradual

decrease in blood level of iodine after the seventh day should answer the question raised by David, Phatak, and Zener <sup>1</sup> regarding possible increased absorption and toxicity through prolonged administration of these drugs. The drugs are probably effective against the trophozoites in the tissues of the intestines and also against the daughter trophozoites arising in the terminal ileum from the metacystic phase of cystic existence, and in this way probably are of value as a prophylaxis as advocated by Craig <sup>10</sup> against *Endameba histolytica* infection when in ameba infested territory. That they destroy cysts as stated by Manson-Bahr <sup>11</sup> seems open to question, but they can probably prevent cyst formation through destruction of the trophozoites.

### SUMMARY

1. Blood iodine studies were conducted on 36 patients who were receiving treatment for amebiasis. Eight patients were given Anayodin with a total of 33 determinations being made. Seven patients received Chiniofon with 27 tests being made. On eight patients receiving Vioform, 31 tests were made. Thirteen patients received Diodoquin as treatment and 49 tests were made. Since these tests were all done in duplicate in order to minimize error, this represents a total of 280 blood iodine determinations.

2. All of the oxyquinoline drugs used in man as amebicides are to some extent absorbed as measured by blood iodine.

3. When considered in terms of milligrams of iodine given, Vioform shows the greatest absorption, Diodoquin second, and Anayodin or Chiniofon the smallest.

4. When given in the recommended therapeutic dosage, Diodoquin gives the highest blood iodine value, Vioform second, and Anayodin or Chiniofon the lowest level.

5. These drugs appear to reach a peak of blood concentration not later than the seventh day and do not appear to be cumulative in absorption or toxicity.

6. If therapeutic value is dependent on iodine absorption, Diodoquin, Vioform, and Anayodin or Chiniofon would rank in the order given in therapeutic effectiveness.

7. Certain factors which may influence absorbability are considered.

8. The question is raised concerning the effectiveness of these drugs in *Endameba histolytica* infection at points other than in the immediate bowel lumen.

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# THERAPEUTIC POSSIBILITIES OF PARA-AMINO-BENZOIC ACID \*

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PARA-AMINOBENZOIC acid (PABA) is generally considered to be a member of the B-complex group of vitamins, and is known to be a constituent of many food substances.<sup>1, 2</sup> Although it is a chemical which has long been known, this substance has been of medical interest only during the past decade. From the available literature, however, the principal interest has been largely confined to studies of its effects on bacterial metabolism, pigment metabolism, and other fields of laboratory investigation. The first important clinical use of PABA was evolved during World War II, when it was found to be of value in the treatment of several of the rickettsial diseases.<sup>3</sup> More recently, a series of studies has been directed toward the investigation of further therapeutic possibilities of PABA. Results have been encouraging in a number of diverse conditions of unknown etiology. For example, a beneficial effect has been noted in lymphoblastoma cutis,<sup>4, 5</sup> in certain forms of lupus erythematosus,<sup>6, 7, 8</sup> in active dermatomyositis,<sup>7, 9</sup> in scleroderma,<sup>5, 9</sup> and dermatitis herpetiformis.<sup>7, 10</sup> In addition, it has been observed that PABA will cause a striking fall in the leukocyte counts of patients with chronic myelogenous leukemia.<sup>11, 12</sup> The purpose of this communication is to review briefly the results obtained with PABA therapy in each of these disorders, and thereby direct attention to the apparent broad range of activity of the compound.

For administration to patients, it has been found that para-aminobenzoic acid (PABA) is best tolerated as a neutral salt. This may be in the form of sodium para-aminobenzoate (NaPAB) † or potassium para-aminobenzoate (KPAB). † The latter form (KPAB) is particularly useful in patients who may develop edema on the sodium preparation. KPAB has been used extensively without evidence of potassium intoxication. It should not be administered, however, in the presence of far advanced renal insufficiency. At present, only NaPAB is available in tablet form. ‡ For this series of studies, PABA was placed in solution by conversion to KPAB with potassium bicarbonate. The final volume was adjusted to make a 10 per cent solution of KPAB. A 10 per cent solution of NaPAB was prepared in a similar fashion. These preparations have a yellow or amber color and

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† The solutions of NaPAB and KPAB administered to the cases reported herein were prepared from crystalline para-aminobenzoic acid which was generously contributed by Merck and Co., Rahway, New Jersey.

‡ Tablets of "PABA Sodium" were kindly supplied for use in these patients by Wyeth and Co., Philadelphia, Pennsylvania.



darken upon exposure to ultraviolet light. The solutions of PABA salts should, therefore, be kept in a dark place, preferably refrigerated. The compounds are administered orally, in doses of one to four grams (10 c.c. to 40 c.c. if the 10 per cent solution is used), at intervals of two to three hours. Most patients prefer to take the solution with a small amount of milk, fruit juice, ginger-ale, or other soft drink. The size of the dose, the total daily dosage, and the intervals between doses are influenced by the size of the patient, by the clinical entity being treated, and by the clinical status of the individual patient. PABA is rapidly excreted in the urine. This is of importance in treating certain disease entities where it is desired to maintain a high blood level of the compound. The optimal dosage schedules have not yet been determined for the several clinical conditions to be discussed below. That there is considerable latitude in the amount of PABA required, however, will be evident from the respective case histories.

### PABA IN LEUKEMIA

Study of the effect of large doses of PABA in patients with leukemia was an outgrowth of the work in rickettsial diseases.<sup>3</sup> The mode of action of PABA on the respective intracellular rickettsial organisms is not completely understood. It appears, however, that PABA inhibits rickettsial multiplication by increasing the metabolism of the parasitized cells.<sup>3, 13</sup> This concept of the mechanism of action of PABA in the rickettsioses led to the thought that cells of disordered metabolic function, i.e., neoplastic cells, might not be able to adapt to a substrate containing PABA in high concentration. The latter hypothesis was tested in patients with leukemia.<sup>11</sup> Briefly, it was found that PABA would lower the leukocyte count in chronic myelogenous leukemia. This effect, however, could be maintained only through the continued administration of large amounts of PABA. Furthermore, concomitant clinical improvement was slight and temporary. For these reasons it was concluded that PABA therapy is not to be considered a practical adjunct to the treatment of leukemia. It is to be emphasized that the same opinion is held at this time. The following case report, hitherto unpublished,<sup>14</sup> is given to illustrate the type of response obtained with PABA in chronic myelogenous leukemia. An additional reason for the selection of this particular case will become apparent in the succeeding section.

### CASE REPORT

A 43 year old white male was admitted to the University Hospital on May 27, 1947, with the chief complaint of pain in the abdomen. During the preceding year there had been a gradual loss of 20 pounds in weight. Ease of fatigue had been present for six months, and symptoms of hypermetabolism for four months. About two weeks prior to admission, the patient experienced the sudden onset of left upper quadrant pain. This was sharp in character and became more severe on inspiration. The

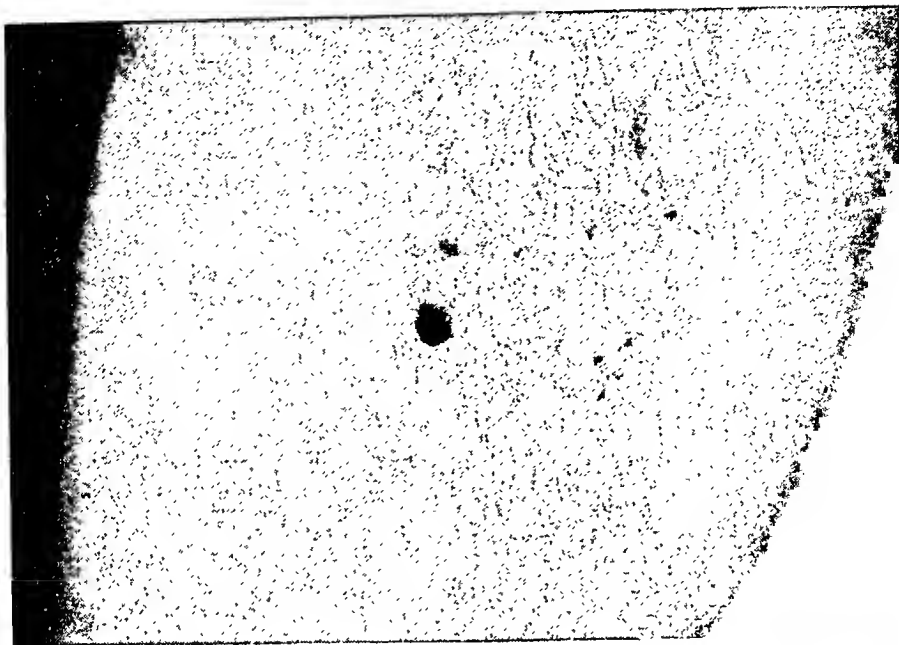


FIG. 1a.



FIG. 1b.

pain radiated to the left shoulder area. He had consulted his physician who referred him to the University Hospital for therapy.

The past history was of no interest except for the occurrence of a skin lesion which appeared on the left thigh in 1927. This lesion was papular and erythematous in nature, and was mildly pruritic. It persisted for several years in spite of treatment and finally disappeared spontaneously. Four years ago a similar lesion appeared on the right calf. This lesion remained essentially unchanged in size and character to the present admission.



FIG. 2a.

Examination of the skin revealed a well demarcated, 6 by 8 cm., raised, erythematous lesion over the medial surface of the right calf (figure 1a). The lesion was superimposed over a mass of varicose veins. Several small lymph nodes were palpable in the axillae and in the inguinal regions. The liver was enlarged to three fingers'-breadth below the right costal margin. It was firm and non-tender. The spleen was very large, extending 20 cm. below the left costal margin in the mid-clavicular line. The remainder of the examination was noncontributory.

Pertinent laboratory findings were as follows: hemoglobin 11 grams per cent; red blood cells 3,500,000; leukocytes 321,000 per cubic millimeter. The white cell differential revealed: 1 per cent basophiles, 2 per cent eosinophiles, 3 per cent lymphocytes, 3 per cent promyelocytes, 32 per cent myelocytes, 17 per cent metamyelocytes and 41 per cent neutrophils, of which 16 per cent were nonsegmented. The basal metabolic rate was + 64 per cent; plasma cholesterol level 112 mg. per cent. Repeated urine analyses showed a small amount of albumin and 6 to 10 white cells per high power field.



FIG. 2b.

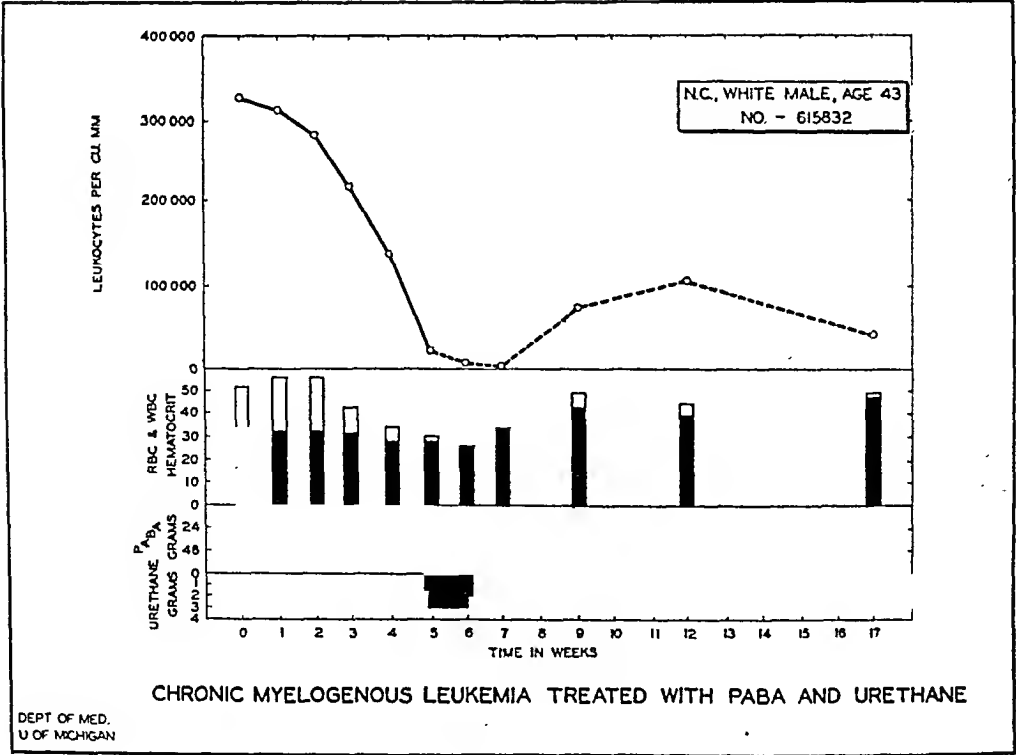


FIG. 3.

After the patient was placed on PABA therapy, a positive test for reducing substances was noted. A biopsy specimen was taken from the skin lesion on the right calf on June 6, 1947. The pathologist reported this to be "premycotic stage of mycosis fungoides; lymphoblastoma cutis" (figure 2a).

While in the hospital the patient was given NaPAB, 4.0 grams every two hours, from June 14, through July 15, 1947. On July 12, the administration of urethane was begun, 3 grams daily. This was discontinued on July 15 because of nausea and vomiting. With this course of therapy, the patient's leukocytes decreased from an initial count of 321,000 to 8,700 per cubic millimeter on July 15. The white cell differential count showed 3 per cent blasts, 9 per cent myeloblasts, 4 per cent metamyelocytes, 19 per cent nonsegmented neutrophils, and 45 per cent segmented neutrophils, 1 per cent monocytes, 10 per cent small lymphocytes, 2 per cent large lymphocytes, 2 per cent eosinophiles, and 5 per cent basophiles. The basal metabolic rate had declined to 34 per cent on July 18. The lesion which was present on the right calf had gradually become flat, the erythema faded, and the pruritus ceased (figure 1b). Another biopsy was taken from an area adjacent to the site of the previous specimen. The pathologist noted "the presence of small perivascular infiltrations which would not have been considered diagnostic without previous knowledge of the case" (figure 2b). The patient was discharged with instructions to resume urethane medication a few days thereafter. This was done and the patient's leukemic process has since been well controlled on urethane therapy. In the accompanying chart (figure 3) are given the patient's leukocyte counts and the red blood cell and white blood cell hematocrit values as related to the administration of PABA and urethane.

### PABA IN LYMPHOBLASTOMA CUTIS

The patient with chronic myelogenous leukemia described above had a localized infiltrated skin lesion which was diagnosed on biopsy as "premycotic phase of mycosis fungoides." This lesion was observed to regress during the period of PABA therapy. Since lymphoblastoma cutis is considered by many to be a primary lymphoblastoma of the skin, it was deemed justifiable to administer PABA to patients with this disorder.<sup>4</sup> The results of therapy in six subjects have been detailed elsewhere.<sup>4, 5</sup> All experienced relief from pruritus and objective improvement of the skin. This was characterized by diminution in erythema and in the degree of infiltration. Treatment with NaPAB was eventually discontinued in four of the cases because of the development of edema. In two patients, however, edema was circumvented by the administration of KPAB with continued improvement. The case presented below was diagnosed from the history and clinical findings as probable lymphoblastoma cutis. It illustrates the character of change which follows KPAB therapy in patients with this disorder.

### CASE REPORT

A 40 year old white male entered the University Hospital on December 13, 1948, complaining of a dermatitis. Ten months previously he had first noted a small, red, scaly, and pruritic area on the lateral aspect of the left ankle. There was a gradual spread of involvement until the entire surface of the body had become red, pruritic, with weeping and crusting. He had consulted a specialist in dermatology who treated

him with superficial roentgen-ray therapy and other measures with definite improvement at first. In late July, 1948, however, the involvement had again become generalized, but the same forms of therapy were then unavailing, and there had been no significant change since.

The past history revealed that the patient had whooping cough at the age of one, following which he was spastic and unable to walk until he was nine years old.

Physical examination revealed an individual with obvious signs of spasticity who appeared chronically ill. There was a generalized erythematous, lichenified, scaling eruption. Small, firm, non-tender, easily movable lymph nodes were palpable in the cervical, axillary, and inguinal regions. The liver was felt two fingers'-breadth below the right costal margin. The edge was firm and non-tender. The remainder of the physical findings were related to the patient's postencephalitic syndrome.



FIG. 4.

Laboratory examination revealed the blood and urine to be normal. After PABA therapy was instituted, however, a reducing substance was detected in the urine. Two biopsies of the skin were taken and two lymph nodes were also removed for histologic study. The skin specimens were reported as psoriasiform eczematoid dermatitis (figure 4). The lymph nodes revealed no definite evidence of lymphoblastoma.

On admission the patient was placed on routine therapy, including starch baths, wet soaks to weeping areas, and calamine liniment. His skin definitely failed to respond to the local measures, however, and pruritus remained a disturbing symptom despite large doses of benadryl. Because of the possibility of a diagnosis of lymphoblastoma cutis, it was decided to undertake a trial of PABA therapy; accordingly, the

patient received 3 grams of potassium para-aminobenzoate every three hours beginning on January 5, 1949. After 10 days, the patient's skin showed definite signs of improvement which was characterized by loss of crusts, cessation of weeping, loss of erythema and infiltration, and diminished pruritus. The patient was discharged from

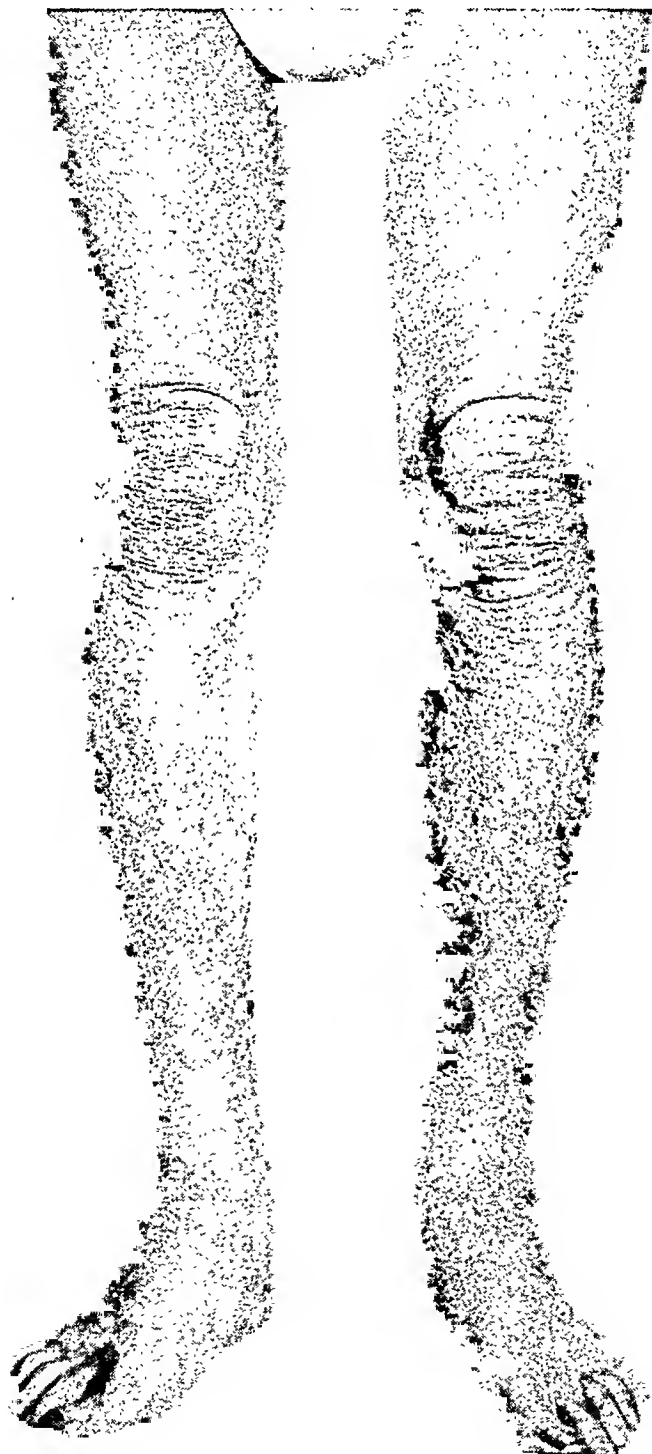


FIG. 5a.

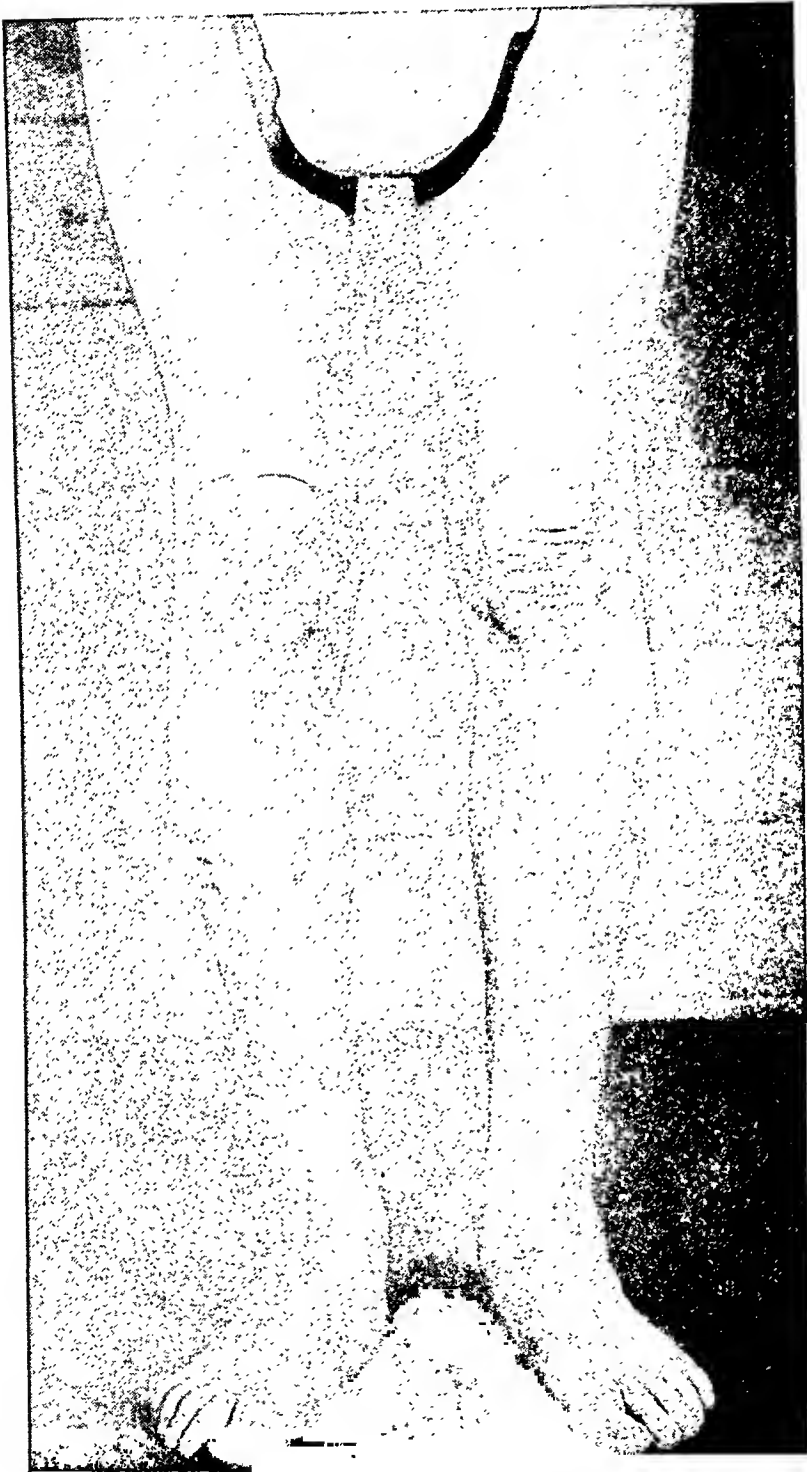


FIG. 5b.

the hospital on January 29, to continue on KPAB, 18 grams daily. The trend of improvement has continued and the program of therapy with KPAB is being maintained at the present writing. The appearance of the patient's legs at the beginning and after eight weeks of therapy is shown in figures 5a and 5b.



## PABA IN LUPUS ERYTHEMATOSUS

Several reports have dealt with the effects of PABA in certain forms of lupus erythematosus.<sup>6, 7, 8</sup> The rationale for administering PABA to patients with lupus erythematosus is based on considerations quite different from those which led to its use in the preceding conditions. There is no general agreement as to the etiology of lupus erythematosus. It is recognized, however, that exposure to sunlight (ultraviolet) may precipitate a relapse or cause an exacerbation of the disease. Sensitivity to sunlight has also been encountered in patients receiving sulfonamide therapy. Since PABA and sulfonamides are metabolically antagonistic, it was reasoned that the former compound might possibly exert a beneficial effect in lupus erythematosus. In view of the experiences in the treatment of the rickettsial diseases<sup>9</sup> and leukemias<sup>11</sup> with large amounts of PABA, it was judged safe to undertake a trial of like therapy in patients with lupus erythematosus. Observations on the effects of PABA in 18 cases of lupus erythematosus have been re-

TABLE I  
Lupus Erythematosus Treated with PABA, Results in 33 Cases

Type of L.E.*	No. of Cases	Clinical Response			
		None	Poor	Good	Excellent
Discoid	10	2	1	6	1
Chronic Disseminated	10	0	1	7	2
Subacute Disseminated	7	1††	1§	4	1
Acute Disseminated	6	4	1	1	0
Totals	33†	7	4	18	4

\* Classified after criteria of Ormsby and Montgomery (1943).

† Totals include 18 cases previously reported in detail.

†† Patient died 4 days after brief course of PABA therapy.

§ Patient died of acute toxic hepatitis on 11th day of treatment; L.E. Lesions clearing at time of death.

ported previously.<sup>8</sup> Since that time 15 additional patients have been treated.<sup>15</sup> An attempt to evaluate the results of therapy in the total of 33 patients is given in the accompanying table (table 1). The classification of the clinical forms of lupus erythematosus is arbitrary and is based on criteria indicated by Ormsby and Montgomery.<sup>16</sup> In addition, it is evident that evaluation of the degree of response to therapy can only be an estimate. Generally speaking, when a response was observed, it was characterized by objective improvement in the cutaneous manifestations. Gradual fading of erythema and diminution of the infiltration and edema were usually noted. In some instances a slight exacerbation of the skin lesions has been noted during the first few days of therapy. Regression of these lesions, however, has followed with continued administration of PABA. Many of the cutaneous lesions disappeared completely. Atrophic, scarred, and telangiectatic

areas, however, were not affected. Subjectively, the patients experienced relief of symptoms of pruritus and/or burning in the involved areas. Some noted improvement in their sense of well-being. One patient had marked alleviation of severe arthralgias. In many instances, prolonged administration of PABA is necessary in order to bring about a clinical response. It should also be emphasized that PABA is not curative and that relapses usually occur after cessation of therapy. The first of the case histories described below will illustrate the result attained during eight months of continuous treatment.

Untoward reactions to PABA therapy will be discussed elsewhere in this presentation. It seems pertinent at this point, however, to note that the incidence of reactions to PABA has been greater in patients with lupus erythematosus than in those with other disorders. This may be a reflection of the already well known fact that patients with lupus erythematosus are hyper-reactive individuals. Occasionally, patients develop hyperpyrexia while receiving PABA. An example of this type of response is given in the second of the cases presented below. It will be seen from the case summary that "desensitization" can be accomplished when this phenomenon is encountered.

#### CASE REPORTS

*Case 1.* A 27 year old white housewife was first seen in the University Hospital outpatient department on July 6, 1948. Approximately one year before the patient had noted the appearance of dusky red papules on the forehead. Shortly thereafter, similar lesions appeared over the entire face and just behind and below the ears. The eruption was more erythematous and became pruritic on exposure to the sun. She had received various forms of therapy for eight months, but the lesions persisted and gradually increased.

On physical examination the abnormal findings were limited to the skin. Scattered over the face were a number of irregularly shaped, discrete, papular, dusky red, scaly lesions which varied in size from 2 mm. to over 1 cm. in diameter (figure 6a).

Laboratory examination revealed a hemoglobin of 12.3 grams per cent and a white count of 8,500 per cubic millimeter, with a normal differential. Urine findings were normal until PABA therapy was begun, at which time a reducing substance was detected. A biopsy specimen was taken from one of the skin lesions and the pathologist observed "slight hyperkeratosis with plugging of dilated hair follicles. Perivascular chronic inflammatory infiltrations are present, and there is slight basophilic degeneration of the collagen in the corium. These findings are compatible with lupus erythematosus, but are not sufficiently advanced to be diagnostic" (figure 7).

The patient was seen in the Dermatology staff conference and the diagnosis of lupus erythematosus was made. Therapy with a mixture of NaPAB and KPAB was begun on July 8, 1948. The patient was instructed to take 18 to 21 grams of medication per day. This program has been continued until the present writing, with the exception of two brief interruptions necessitated by the appearance of nausea and vomiting. During the course of treatment the lesions have shown progressive improvement, as is evident in the accompanying photographs (figure 6b).

*Case 2.* A 21 year old trained nurse was admitted to the University Hospital on February 5, 1949. She had experienced severe episodes of sunburn during the summer of 1947 and of 1948. In September, 1948, the patient noticed that the skin of each forefinger had become dry and cracked. Within a period of three weeks,



FIG. 6a.



FIG. 6b.



FIG. 7.

pain and swelling appeared in all the fingers. Gradually, the wrists, elbows, shoulders, knees, ankles and toes became similarly involved. She began to have low-grade fever. Periorbital swelling and erythema were also observed. The degree of erythema became more marked on exposure to sunlight. The patient was hospitalized elsewhere three times in November and December, 1948. Treatment consisted of bed rest, aspirin, vitamins, quinine, and intramuscular injections of bismuth. Despite attempts at therapy, however, her condition became worse. Two blood transfusions were administered and the patient was started on NaPAB therapy, 2 grams every three hours, in mid-December. The patient became more severely ill with chills, fever, increased edema, pain, weakness, and rapid pulse. On December 30, the temperature rose to 106° F.; NaPAB was discontinued, penicillin was administered, there was gradual improvement, and the fever fell to its previous level of 100° to 101° F. After two weeks NaPAB was begun again but was discontinued after the second dose because she developed a severe chill and the temperature became elevated to 104° F. Two

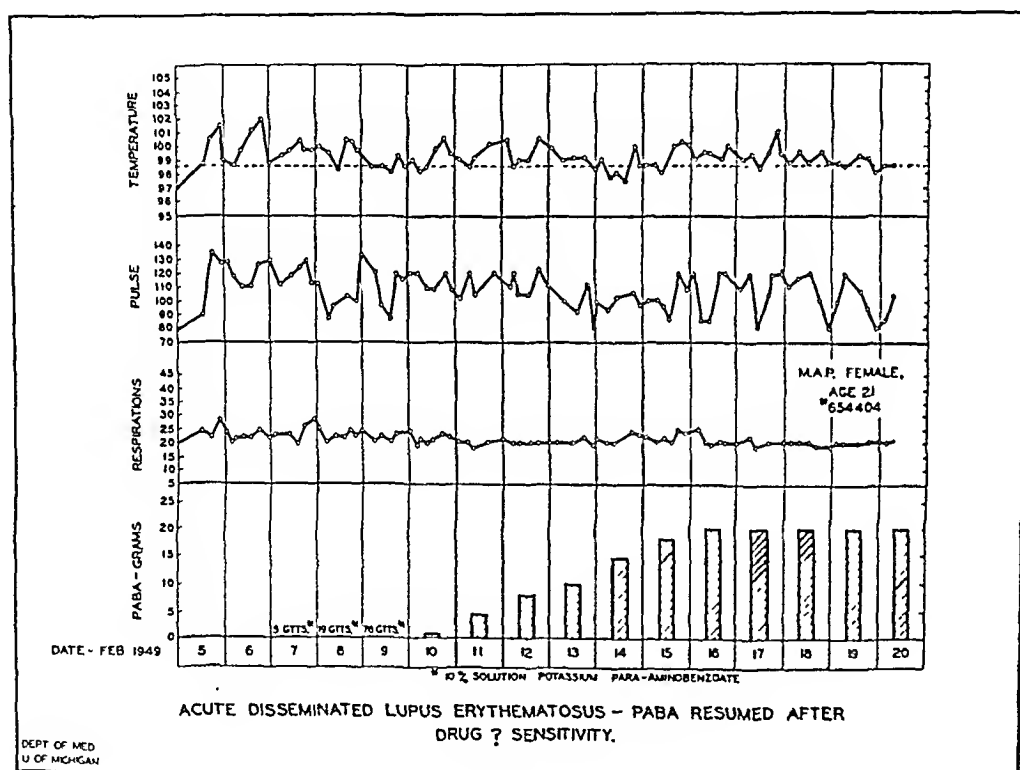


FIG. 8.

days later one dose of 2 grams of NaPAB was administered with similar results. This compound was discontinued entirely and after additional transfusions, the patient was discharged home to remain at bed rest until her admission to this hospital.

Examination revealed a well developed white female in no acute distress. The temperature was 100.8° F.; pulse rate was 136 per minute; respirations were slightly increased. The skin was dry with erythematous areas about the eyes and over each elbow. Periorbital edema was present bilaterally. There were small erythematous nodules over the palmar aspects of her fingers at the interphalangeal joints. A small ulceration was noted on the right border of the tongue. A blowing systolic murmur was heard over the apex. Except for the presence of bilateral inguinal adenopathy, the remainder of the examination was normal.

Laboratory findings revealed normal hemoglobin and red blood cell values (history of recent transfusions). The leukocytes numbered 5,200 per cubic millimeter with a normal differential. Examination of the urine revealed no abnormalities; however, after PABA therapy was instituted, a reducing substance was detected in each specimen. The blood nonprotein nitrogen was 28 milligrams per cent.

The patient's history clearly indicated that the administration of PABA had induced bouts of hyperpyrexia. It was, therefore, decided to begin with minute quantities of the compound in an effort to bring about "desensitization" to PABA. Accordingly, on February 7, 1949, the patient was given 1 drop of a 10 per cent solution of potassium para-aminobenzoate, and this dose was repeated every three hours. As there was no reaction, the quantity was gradually increased and by February 15, the patient was tolerating 25 c.c. (2.5 grams) of the compound every three hours. The patient's fever gradually subsided to near normal levels (see figure 8). Concomitantly, there was subsidence of muscle and joint pains, and the patient was allowed to sit up in a chair for brief intervals. She was discharged on February 20, to continue on KPAB, 21 grams per day. On a return visit two weeks later, the patient's general condition was about the same. Anemia was now evident as she had received no further transfusions. She was, however, tolerating the full amount of PABA which had been prescribed.

### PABA IN DERMATOMYOSITIS

The utilization of PABA in dermatomyositis stems from the foregoing investigations with lupus erythematosus. It will be recalled that the rationale for the use of PABA in the latter condition was based on the factor of ultraviolet light sensitivity. In view of the observed response in patients with lupus erythematosus, it was reasoned that PABA should be given a trial in other disorders which have associated light sensitivity. Hypersensitivity to light is not generally associated with dermatomyositis. One patient with this condition, however, stated that exposure to sunlight aggravated the discomfort in the involved skin areas. Since she was becoming rapidly worse on other attempts at therapy, PABA therapy was undertaken in accordance with the thoughts indicated above. The dramatic result of treatment in this patient has been given elsewhere.<sup>9</sup> The same authors have now treated five patients with features of dermatomyositis, and there has been one death in the group.<sup>17</sup> The remaining four patients have all improved. The first patient to receive PABA for dermatomyositis is still living and active. She has been maintained for 18 months on KPAB. Presented below is the case summary of another patient who is being treated for dermatomyositis.

### CASE REPORT

A 38 year old white female had been well until May, 1947, when there appeared edema of the forehead, eyes, and cheeks, associated with erythema of the skin of these areas. This difficulty subsided after a period of two months and she remained in remission until February, 1948. At that time, pain, swelling, redness, and limitation of motion occurred in the knees, ankles, shoulders, elbows, wrists and fingers. This involvement persisted until the time of admission to the University Hospital on September 22, 1948. In addition, she had intermittently a pruritic, tender, erythematous eruption on the palms, soles, and over extensor surfaces of the hands, arms,

and legs. The patient had been continually febrile for at least seven months and had lost 17 pounds in weight. Anorexia, general malaise, and weakness were prominent complaints. She had been seen at the Mayo Clinic in July, 1948, where the diagnosis of dermatomyositis was made.

On examination, the patient appeared to be chronically ill. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic; pulse 110; respirations 20; temperature 101.4° F. A faint erythema and scaling was present on the extensor surfaces of the arms and hands, and on the anterior tibial surfaces. There was limitation of motion of the elbows, wrists, knees, and the interphalangeal joints. The latter were swollen and tender, as were both wrists. The liver was palpable 3 cm. below the right costal margin, while the spleen could be felt 2 cm. below the left costal margin. Neither organ was tender. The remainder of the physical examination was negative.

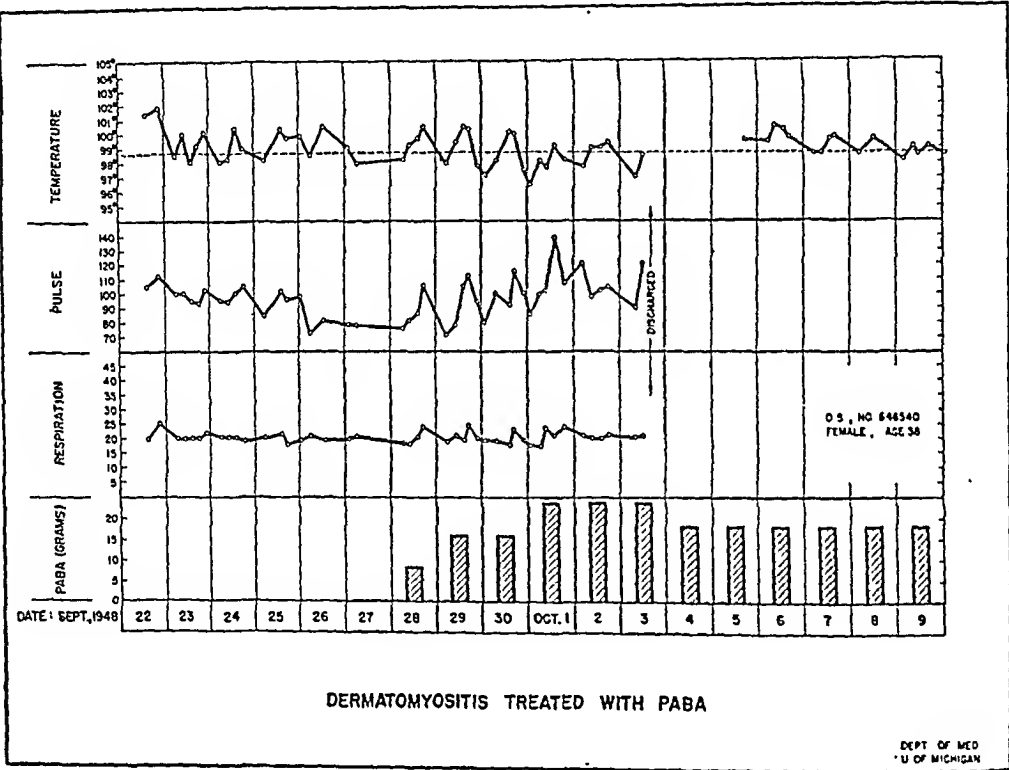


FIG. 9.

Admission blood and urine findings were not remarkable except for a hemoglobin of 12 grams per cent. The 24 hour urinary creatine excretion was found to be 760 milligrams on September 23. An ultraviolet skin sensitivity test showed the patient to be three times as sensitive as normal. Muscle and skin biopsies were taken from the left pectoral area. Microscopic examination revealed slight perivascular monocyctic infiltrations in the dermis. More marked perivascular monocyctic infiltration was present in the subcutaneous adipose tissue and in voluntary muscle. The pathologist interpreted these findings as being compatible with the diagnosis of angiomysitis.

After the preliminary studies were concluded the patient was placed on PABA therapy, 2 grams every three hours initially. There was a gradual fall in temperature towards normal (figure 9) and the patient felt subjectively improved. She was discharged on October 3 to continue on 18 grams daily of KPAB, and to return for monthly check-ups. By mistake the patient took two times the prescribed amount of drug and had a severe gastrointestinal upset. After a few days, however, therapy

was resumed at 12 grams daily. The patient has continued on this program to the present time. She has been afebrile since mid-October, 1948. Appetite, strength and sense of well-being have gradually returned. The joint involvement subsided markedly but there has been residual stiffness, which, however, is also improving.

### PABA IN SCLERODERMA

Lupus erythematosus, dermatomyositis, and scleroderma are often grouped together as "diffuse collagen disorders."<sup>18</sup> It was natural, therefore, that the studies of the effects of PABA in the former conditions should lead to a desire to test its value in patients with scleroderma. An added stimulus arose during the course of PABA therapy of a patient who had features of both dermatomyositis and scleroderma. Since the patient showed remarkable improvement in both aspects of his condition, the transition to therapy in scleroderma was enhanced. The results of treatment in this patient and four additional cases of scleroderma have been described.<sup>9</sup> Improvement occurred in all, and was greater when the involvement was extensive. The sclerodermatous areas gradually softened and became thinner and more pliable. There was a consequent increase in range of motion of affected parts. In some patients there has been observed a definite decrease of pigment in previously hyperpigmented areas. The administration of PABA salts has been extended to additional cases of scleroderma.<sup>17</sup> Summaries of the records of two of these patients are given below. The first patient represents more or less the classical picture, whereas the second case emphasizes the fact that visceral involvement is a common accompaniment of scleroderma. An interesting therapeutic problem arises in connection with the intestinal involvement exemplified by the second patient. It is likely that there is softening of the wall of the intestinal tract during KPAB therapy just as softening of the skin occurs. Conceivably, this might precipitate marked intestinal dilatation with signs of ileus. For this reason, it is believed that all patients with scleroderma should have a complete roentgenologic examination of the gastrointestinal tract prior to the institution of treatment with PABA. In the event widespread small bowel involvement is encountered as in the case below, treatment should be cautiously undertaken. In the light of present knowledge, it seems best to begin with small doses (e.g., 4 to 6 grams per day). Subsequently, the dosage schedule may be augmented as the patient's progress warrants.

### CASE REPORTS

*Case 1.* A 40 year old white housewife was admitted to the University Hospital on September 9, 1948. One year before she had noted the onset of numbness and tingling in the fingers. Later the fingers became swollen and it was necessary to have her wedding band cut off. In the six months preceding admission to the hospital, there had been a gradual increase in pigmentation of the skin, especially over exposed parts. In addition, there had been progressive weakness and a weight loss of 40 pounds despite a fair appetite. More recently she had noticed a sensation of

tightness and swelling in the lower legs. The patient also complained of episodes of substernal burning which had occurred since March, 1947. These attacks of discomfort usually appeared at night while lying in bed. There were no other signs or symptoms referable to the gastrointestinal tract.

On physical examination the patient appeared chronically ill. There was a diffuse hyperpigmentation over the face, anterior sternal area, the forearms and hands. The skin over the forehead was somewhat atrophic and bound down, as was the skin over the clavicles and over the dorsal aspects of the hands. There was swelling of the proximal interphalangeal joints with limitation of motion. Dependent cyanosis of the finger tips was noted. The skin of the lower extremities showed similar changes to those noted in the hands. The liver was palpable 5 cm. below the right costal margin in the midclavicular line. The remainder of the examination was negative.

Laboratory findings included the following: hemoglobin 12.0 grams per cent; leukocytes 13,400 with a normal differential; repeated urine analyses were negative except for the appearance of a reducing substance when the patient received PABA therapy. The urine creatine excretion was 0.48 gram for the 24 hours of September 8. An ultraviolet skin sensitivity test revealed the patient to have two times the



FIG. 10a.



FIG. 10b.

normal sensitivity. A punch biopsy specimen was taken from the skin of the hand and was histologically compatible with a diagnosis of scleroderma. Roentgen examination of the hands revealed cystic osteoporosis, more marked in the left carpal bones, with destruction of the distal ends of the terminal phalanges of the three middle digits of the right hand. A roentgen-ray examination of the upper gastrointestinal tract was negative.

While in the hospital the patient was started on a 50-50 mixture of NaPAB and KPAB, 2 grams every three hours. Therapy was well tolerated and the patient was discharged on September 23 to continue with six doses a day of 3 grams each. When next seen on October 1, there had been very evident softening of the involved skin areas. Treatment was continued until October 7, at which time the patient developed





FIG. 11a



FIG. 11b.

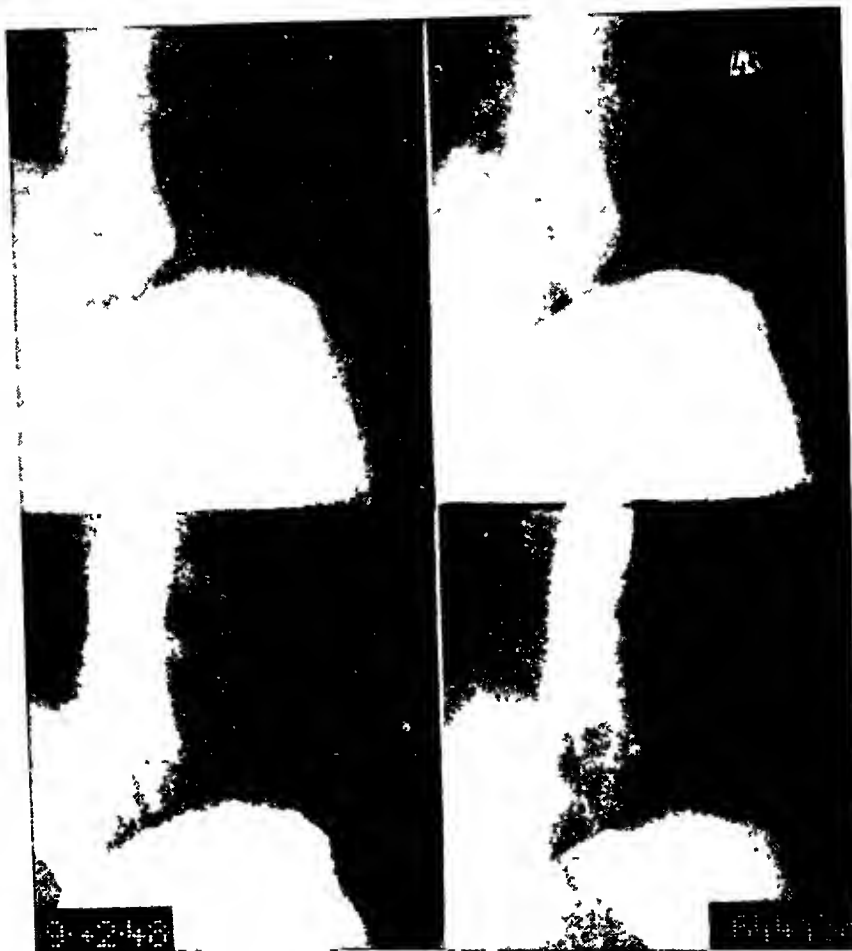


FIG. 12

nausea, vomiting and fever. PABA was discontinued until December 3 when it was resumed at five drops each three hours. As there was no reaction, the dose was progressively increased on succeeding days. By December 10, the patient was taking 6 grams daily. The amount was gradually increased and the patient has averaged 12 grams daily to the present writing. In addition to the softening of the skin, there has been depigmentation (figures 10a and 10b). The patient is also experiencing less retrosternal discomfort.

*Case 2.* A 50 year old white housewife was admitted to the University Hospital on August 19, 1948. For five or six years she had had considerable discomfort from epigastric burning with frequent nausea and vomiting. Since January, 1948, the



FIG. 13.

patient had experienced greater distress with cramping pains, distention, and constipation. The vomitus was observed to contain food ingested the previous day. There had been a gradual weight loss of 20 pounds. Tightness of the skin of the face, fingers, and hands had been present for several years and was progressing slowly. A rash had appeared on the face a few months prior to admission to the hospital.

Examination revealed an erythematous, scaling, crusted eruption on the skin of the forehead, face and behind the ears. The skin was thickened on the face, neck, arms, hands and shoulder-girdle. There was limitation of motion of the fingers, and the mouth could not be opened widely (figure 11a). The abdomen was greatly distended and tympanitic. A succussion splash was present. The remainder of the physical examination was within normal limits.

Laboratory examination revealed the urine and stool to be normal. The hemoglobin was 12.7 grams per cent. The leukocytes numbered 2,400 per cubic millimeter

with the following differential count: 41 per cent neutrophils, 2 per cent eosinophils, 29 per cent large lymphocytes, 20 per cent small lymphocytes, and 8 per cent monocytes. The 24 hour urinary creatine excretion was 660 milligrams. An ultraviolet skin sensitivity test revealed the patient to have three times the normal sensitivity. Roentgen examination of the gastrointestinal tract revealed a normal colon. There was a cuff-like narrowing of the distal esophagus (figure 12) and profound neuromuscular abnormality of the small bowel. A skin biopsy specimen was taken from the dorsal aspect of the right forearm and revealed homogenization of fibrous connective tissue in the dermis (figure 13).



FIG. 14.

Initial treatment was directed toward relief of the partial intestinal obstruction. Wangensteen suction was instituted and decompression accomplished. There was gradual relief of symptoms, and PABA therapy was begun on September 2. From 18 to 24 grams daily were administered during the first weeks of treatment.

On this regimen, the patient's skin softened slowly and became loose at the previously hide-bound areas. The patient was able to open her mouth more widely (figure 11b), and the eruption on the face cleared. Episodes of abdominal distention and constipation continued but were less frequent, and nausea and vomiting no longer occurred. Another gastrointestinal roentgen-ray examination was performed on November 24. It revealed loss of gastric and esophageal peristaltic activity

and profound disorder of small bowel function. This was evidenced by the extremely dilated loops of jejunum and duodenum with greatly delayed passage of barium. The opaque medium was still in mid-jejunum at five hours (figure 14). In view of these findings, it was decided to continue with PABA therapy but at a reduced dosage of 6 to 9 grams daily. The patient has tolerated this medication with continued improvement in gastrointestinal function and of the cutaneous manifestations. Concomitantly, there has been a definite gain in strength with ability to resume her household activities.

### PABA IN DERMATITIS HERPETIFORMIS

Para-aminobenzoic acid administered in large amounts has also been shown to suppress the manifestations of dermatitis herpetiformis.<sup>7, 10</sup> This disorder is usually well controlled with sulfapyridine or Asiatic pills.<sup>18</sup> Occasionally, however, forms highly resistant to the usual treatments are encountered. The first patient to receive a trial of PABA therapy for dermatitis herpetiformis was severely afflicted and had not responded to other medications.<sup>10</sup> The reason for trying PABA in that particular patient was the fact that exposure to sunlight caused more intense pruritus of the lesions. In the five cases reported elsewhere, improvement was observed in all.<sup>10</sup> Usually there was complete disappearance of bullae and other skin lesions. In some instances, a few scattered lesions remained. Pruritus gradually subsided and then disappeared. It is of interest that the process recrudesced about 8 to 10 days after cessation of PABA therapy. Upon resumption of treatment, control of the lesions is reestablished. In the patients so far observed, continued suppression requires continued administration of PABA. The following case report illustrates the effect of PABA in dermatitis herpetiformis.

#### CASE REPORT

A 78 year old white female was admitted to the University Hospital on July 9, 1948. Eight weeks previously, her eyelids and lips had become swollen. On the following day, a pruritic red rash appeared in the left antecubital space. She had taken no unusual medications at the time of onset. Within two or three weeks, the erythematous eruption had spread to involve both arms, the abdomen, lower back, thighs, and legs. Bullae appeared on the arms. Pruritus was intense.

On examination the pertinent findings were limited to the skin. Infiltrated, erythematous, plaque-like lesions were present on the lower arms, chest, abdomen, lower back, buttocks, and thighs. Several large bullae were present in the left antecubital space. The largest of these was 2.5 cm. long and 1.5 cm. wide, and contained a clear, straw-colored fluid. All of the bullae were tense. There were no mucous membrane lesions.

Laboratory examinations revealed the urine to be normal. Blood values were within normal limits except for a slightly elevated white count of 11,360 per cubic millimeter. The differential count revealed 6 per cent eosinophiles but was otherwise not remarkable.

The patient was treated with wet dressings, calamine liniment, and daily liquor carbonis detergens baths. The diagnosis of dermatitis herpetiformis was made and sulfapyridine, 0.5 gram, four times daily was started on July 12. This was discontinued on July 15 because of nausea. On July 20, administration of potassium para-

aminobenzoate, 1 gram every three hours, was begun. This was gradually increased over the next three days to 3 grams at three hour intervals for five doses. The patient also received superficial roentgen-ray therapy. On this regimen, the lesions gradually regressed and there was only residual hyperpigmentation at the time of discharge on August 15. The KPAB dosage schedule had been reduced to 6 grams daily on August 10. Within 10 days lesions began to reappear. The amount of KPAB was increased to 18 grams daily and the lesions again subsided. Activity of the process in this patient appears to be suppressed by 15 to 18 grams daily of the compound. This program of therapy is being continued at the present writing.

## DISCUSSION

The clinical course of an individual patient who has one of the foregoing disorders may be unpredictable. It is believed, however, that sufficient patients in each group have been treated with para-aminobenzoic acid to allow a preliminary evaluation. It appears quite evident from the data available that the causal relationship between therapy and response has been too consistent to be attributed to chance remission. That the improvement observed in these patients is due to the administration of PABA is further supported by the fact that relapse usually occurs after cessation of therapy.

The response observed in patients with chronic myelogenous leukemia does not justify the use of PABA in patients with leukemia. In regard to the remaining entities, however, it is believed that PABA may be of value in selected cases. It will be recalled that in these patients all of the usual forms of therapy had been tried and abandoned before PABA therapy was instituted. The most gratifying results have so far been attained in lymphoblastoma cutis, scleroderma, and certain cases of dermatomyositis. Results of therapy in acute disseminated lupus erythematosus have been disappointing as may be noted in the accompanying table. On the other hand, there has been sufficient benefit noted in two cases of the acute form to warrant trial of PABA in additional patients. Dermatitis herpetiformis is usually controllable with other forms of medication. In instances of intolerance to the usual treatment, however, para-aminobenzoic acid therapy may be used.

The mode of action of PABA in these diverse conditions is not known. All of the disorders are of unknown etiology and the pathogenesis of each is poorly understood. It is, therefore, unprofitable to speculate at this time as to the possible mechanisms involved. Surely the diseases referred to above cannot be considered to result from PABA deficiency, since the dosages employed are far greater than the trace amounts required for physiologic vitamin-enzyme activity.<sup>19</sup>

A number of toxic manifestations have been encountered during PABA therapy. The most serious of these was a fatal case of toxic hepatitis.<sup>8</sup> In addition, drug fever and dermatitis medicamentosa have been observed. When drug fever appears, it is possible to "desensitize" the patient as was illustrated in one of the case reports above. It has already been noted that an initial exacerbation of the skin manifestations of lupus erythematosus is

sometimes seen. It also appears worthy of interest that the preponderance of reactions to PABA have occurred in the lupus erythematosus group of patients.

Nausea, at times associated with vomiting, is the most frequent reaction. This usually subsides after omission of a few doses of the drug. Therapy has often been resumed in such cases without further difficulty.

Leukopenia may be present in patients who are receiving PABA. It is difficult to decide whether this is due to the compound, since several of the above named conditions are characterized at certain stages by a low white blood cell count. There have been no cases of agranulocytosis from PABA. In the light of experiences with other substances, however, it is possible that this might occur rarely in patients receiving PABA. This possibility should be kept in mind.

A reducing substance has been detected in the urine of all patients taking large amounts of PABA. This was believed to be glucose as a result of findings with osazone and other tests.<sup>11</sup> Additional studies have given evidence that this may not be glucose.<sup>20</sup> This finding raises certain implications not hitherto recognized. It is especially important in that at least two instances of hypoglycemic attacks have been observed during the administration of PABA.<sup>17</sup> Through investigations now in progress it is hoped to explain these observations.

From the studies referred to herein, it is concluded that para-aminobenzoic acid has therapeutic possibilities in several diseases of unknown etiology. These are lymphoblastoma cutis, certain forms of lupus erythematosus, dermatomyositis, scleroderma, and dermatitis herpetiformis. Apart from the immediate practical considerations, it is hoped that additional study of the effects of para-aminobenzoic acid will yield information as to the mechanisms involved in these obscure disorders.

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# GONOCOCCAL ARTHRITIS: A STUDY OF 202 PATIENTS TREATED WITH PENICILLIN, SULFONAMIDES OR FEVER THERAPY \*

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PRIOR to March, 1932, only symptomatic measures were available for the treatment of gonococcal arthritis. At that time, it was observed during a course of fever therapy for syphilis that the gonococcal arthritis also present had improved.<sup>1</sup> Further studies confirmed this original observation and fever became the accepted form of therapy. Several years later the sulfonamides were introduced and most recently penicillin became available. Since these three methods of treatment have received extensive trial at the Gallinger Municipal Hospital, it appeared worthwhile to review these cases. They have been analyzed in the present paper, with particular reference to the efficacy of these three methods of treatment.

## SELECTION OF CASES

The charts of all patients discharged with the diagnoses of gonococcal arthritis from January 1936 through November 1947 were reviewed. Criteria for including a patient in this study were similar to those suggested previously by Spink and Keefer.<sup>2</sup> In the presence of inflammatory rheumatism the diagnosis was considered definite if organisms morphologically resembling gonococci were found on smear or culture of the joint fluid. This was particularly true if the organisms were also found by smear or culture of exudate from the genitourinary tract. The diagnosis was considered probable in the absence of positive bacteriologic findings in the joint fluid, provided the organisms were found in specimens taken from the genitourinary tract and other studies did not indicate another type of arthritis. Similarly a positive complement-fixation test was accepted as probably diagnostic in the absence of positive bacteriologic findings in the joint fluid or the genitourinary tract, when other forms of arthritis were ruled out.

It is our opinion that the complement-fixation test is reliable for the establishment of the diagnosis of gonococcal arthritis since about 80 per cent <sup>3-6</sup> of patients with gonococcal arthritis have a positive complement-

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We wish to thank the members of the Genitourinary Service for opportunity to study two of these cases, and Miss Joan Rowe and Miss Myrtle Myer for technical assistance.



fixation test in the blood or joint fluid. In chronic gonorrhea the test is positive in only 35 per cent and almost invariably negative during the acute stage of gonorrhea. Muether and Andrews<sup>7</sup> stated that they rarely found false positives while false negatives do occur occasionally. In our series, the complement-fixation test was done on the joint fluid or blood in 99 patients and was found to be positive in 81 (82 per cent). In 30 instances, there was other confirmatory evidence of a gonococcal infection.

Even though there was a history suggestive of recent gonococcal infection, the case was not included in our series unless the above criteria were fulfilled. Patients were included in the series, however, even in the absence of a history of gonorrhea. We believe that the inability to elicit a history of gonorrhea is of little value in excluding gonococcal arthritis because of the long interval which may intervene between the genitourinary infection and the arthritis<sup>8, 9</sup> and the difficulty of establishing the diagnosis in females.

#### AGE, SEX AND JOINT INVOLVEMENT

Included in our series are 109 (53.9 per cent) males and 93 (46.1 per cent) females. Others<sup>3</sup> have stated that the incidence of gonococcal arthritis in males is four to five times that in females.

Eighty-five per cent of the cases occurred between the ages of 20 and 40 in the males, and between the ages of 10 and 30 in the females.

TABLE I  
Joints Involved in 202 Cases of Gonococcal Arthritis

Joint	Monarticular 39 Patients	Polyarticular 163 Patients
Knee	23	162
Ankle	3	126
Wrist	9	69
Shoulder	1	56
Hip	1	56
Elbow	1	51
Feet and toes	0	38
Hands and fingers	0	26
Thoracic and lumbar spine	1	8
Cervical spine	0	7
Sternoclavicular	0	7
Temporomandibular	0	3

Gonococcal arthritis is usually a polyarticular disease<sup>3, 5, 10-12</sup> although it is frequently stated that it is monarticular in involvement. A possible explanation for this belief is the fact that after a period of migratory arthritis, in which most of the joints are only slightly affected, the involvement persists in one of the joints, particularly one involved early in the disease. In our series, monarticular involvement occurred in only 39 patients, while 163 had polyarthrititis. In table 1 the incidence of involvement of the various joints is tabulated.

## RESULTS OF TREATMENT

The duration of the infection prior to the time of treatment was determined for each patient and correlated with the response to therapy. On this basis it was found that the patients could be grouped into those whose symptoms were less than 30 days' duration, and those treated after the thirtieth day. For purposes of classification the former were designated as "acute" and the latter as "chronic."

The response to treatment was evaluated solely on the basis of freedom from evidence of infection rather than upon the functional result. There are many patients who are cured of the infection but remain crippled as a result of the disease.

*Symptomatic Treatment.* Eleven patients who were admitted during the period of study received only symptomatic treatment. Nine recovered and two were discharged against advice, on the second and eleventh hospital days, respectively, without improvement. Although some patients with gonococcal arthritis recover spontaneously, these results are obviously not indicative of the efficacy of this method of therapy. These patients happened to improve while they were undergoing diagnostic studies before specific therapy was instituted. By contrast, there were numerous patients being studied who did not improve until specific therapy was instituted.

*Fever Therapy.* A course of fever therapy was given to 55 patients. Fever was induced by two methods, radiant energy (Kettering hypertherm), and typhoid vaccine intravenously. The results of these two methods were so different that they will be discussed separately.

An adequate course of therapy in the Kettering hypertherm consists of at least four sessions at three to five day intervals during which time a temperature of 106° F. to 106.5° F. is maintained for six hours.<sup>10, 13, 14</sup> In our patients treated by this method, therapy appeared to be adequate in 33 patients, 21 (63.6 per cent) of whom recovered. When the cases were divided into "acute" and "chronic" varieties, it will be seen from table 2 that 77 per cent of the patients treated during the "acute" stage recovered, whereas, only 55 per cent of those in the "chronic" stage responded favorably.

It is obvious that the prognosis was much more favorable in those treated promptly. This difference in the response of the "acute" and "chronic" cases to hyperthermia has been noted by many investigators.<sup>3, 10, 11, 13-15</sup> There appeared to be no difference between the results in the "chronic" patients who became "chronic" while receiving other treatment unsuccessfully and in those who procrastinated in presenting themselves for therapy.

Previous attacks of arthritis did not influence the outcome of treatment with the hypertherm cabinet. Ten of the 16 patients who had previous arthritis recovered, compared with 11 out of 17 with no previous attacks.

Of the 22 patients given typhoid vaccine intravenously 10 (45.4 per cent) had a favorable response. These patients were in the "acute" stage. Eight with "acute" and four with "chronic" infections failed to respond. These

data are shown in table 2. Although these results appear disappointing, they probably do not represent an accurate picture of what can be expected from this form of therapy. An accepted technic consists of sessions during which a temperature of 105° F. to 106° F. is maintained for two to five hours<sup>16</sup> plus the proper use of diet, sedation and accessory heat in the form of blankets and hot-water bottles. If the injection of 50 to 100 million organisms does not produce a temperature of 102° F. within two hours, another injection of 50 to 100 million organisms should be given. This may be repeated again in an hour or two if necessary in order to achieve the proper febrile response. After careful review of the plan of therapy in each of our cases in no instance could the technic be classified as adequate.

TABLE II  
Results of Therapy in Gonococcal Arthritis

Type of Therapy	Acute Arthritis						Chronic Arthritis						All Cases		
	With Previous Arthritis		Without Previous Arthritis		Total		With Previous Arthritis		Without Previous Arthritis		Total				
	R*	F†	R	F	R	F	R	F	R	F	R	F	R	F	
Fever	Cabinet	4	1	6	2	10 (77%)	3	6	5	5	4	11 (55%)	9	21 (63.6%)	12
	Typhoid vaccine	4	4	6	4	10 (55.5%)	8	0	3	0	1	0 (0.0%)	4	10 (45.4%)	12
Sulfonamides ‡		16	12	66	15	82 (75.2%)	27	3	13	12	3	15 (48%)	16	97 (69.3%)	43
Penicillin		0	3	21	5	21 (72.4%)	8	0	1	2	0 ‡	2 (66.7%)	1	23 (71.8%)	9

\* Recovered from all evidences of the infection.

† Failed to recover from the infection during the period of treatment.

*Sulfonamide Therapy.* Of the 140 patients treated with sulfonamides 97 patients (69.3 per cent) recovered (table 2). In order to determine the effectiveness of the sulfonamides several factors had to be considered: (1) the duration of the infection, (2) a history of previous attacks of arthritis, (3) the particular sulfonamide employed, (4) the total dose administered, and (5) the duration of therapy.

Sulfanilamide was employed in 63 patients, sulfapyridine in 19, sulfathiazole in 36, sulfadiazine in 15, and sulfamerazine in 7. These results are tabulated in table 3 and since the results with each sulfonamide are essentially the same, the sulfonamides will be considered as a whole.

Early treatment played a significant part in the response to therapy. Recovery occurred in 82 (75.2 per cent) of those patients who were treated within 30 days of the onset of the arthritic symptoms, whereas 15 (48 per

cent) recovered who were treated after the lapse of the 30 day period (table 2). The occurrence of previous arthritic attacks appears to be an even more significant factor. The results in the group of patients who gave no history of previous attacks of arthritis are similar whether treated "early" or "late." On the other hand, in those patients with a previous arthritic history there is a pronounced difference in the response to sulfonamides. A favorable response occurred in 16 (57 per cent) out of 28 patients in the "acute" group, whereas only three (19 per cent) out of 16 recovered in the "chronic" group. These differences are statistically significant.

TABLE III

Results of Sulfonamide Therapy in Gonococcal Arthritis, Arranged According to the Individual Drugs Used and the Year of Treatment

	1938		1939		1940		1941		1942		1943 to 1946		Total	
	R*	F†	R	F	R	F	R	F	R	F	R	F	R	F
Sulfanilamide	17	2	10	4	18	9	1	1	1	0			47 (75%)	16
Sulfapyridine			1	0	4	5	3	2	2	2			10 (53%)	9
Sulfathiazole					2	2	16	2	6	4	2	2	26 (72%)	10
Sulfadiazine							0	2	5	1	4	3	9 (60%)	6
Sulfamerazine											5	2	5 (72%)	2
Total	17 90%	2	11 73%	4	24 60%	16	20 74%	7	14 67%	7	11 61%	7		

\* Recovered from all evidences of the infection.

† Failed to recover from the infection during the period of treatment.

It has been suggested that in acute gonorrhea the sulfonamides are becoming progressively less effective as a result of inadequate therapy and the consequent development of resistant strains of gonococci. Thus it was deemed necessary to calculate the total amounts of sulfonamides utilized by the patients in this series. Whereas, during the year 1938 the average total dose ranged from 30 to 39 grams, the average doses employed in 1940 varied from 60 to 69 grams. The explanation for the maintenance of the recovery rate in the later years may have been the increased dose of sulfonamides. The increase in total dosage not only represents an increase in the amount but also in the duration of therapy. In table 4 it can be seen that in the later years therapy was continued for a longer period of time. Figure 1 graphically presents the results of sulfonamide therapy in relation to the duration of

TABLE IV  
Results of Sulfonamide Therapy in Gonococcal Arthritis  
Arranged According to the Duration of Therapy

Days	1938		1939		1940		1941		1942		1943 to 1946		Total		Per Cent Re- covered
	R*	F**	R	F	R	F	R	F	R	F	R	F	R	F	
0-3	1	1	1	0	0	3	0	2	0	0	0	0	2	6	25.0
4-6	4	0	3	1	6	5	1	2	1	1	1	1	16	10	61.5
7-9	5	1	3	2	5	1	5	2	5	1	3	1	26	8	76.4
10-12	1	0	1	0	5	3	5	0	2	3	4	1	18	7	72.0
13-15	2	0	2	0	1	1	2	0	2	0	1	1	10	2	83.3
16-18	1	0	1	0	2	0	1	1	3	2	0	1	8	4	66.7
19-21	1	0	0	0	0	1	3	0	1	0	2	1	7	2	77.7
21	2	0	0	1	5	2	3	0	0	0	0	1	10	4	71.4

\* Recovered from all evidences of the infection.

\*\* Failed to recover from the infection during the period of treatment.

therapy. The best results were obtained in patients treated for nine days or more.

*Penicillin Therapy.* We have treated 32 patients with penicillin since the introduction of this antibiotic, 23 (71.8 per cent) recovered. Fourteen of these cases have previously been reported.<sup>17</sup> These results are not an accurate representation of the value of penicillin, however, since among the nine failures three patients were treated with a total dose of 300,000 units

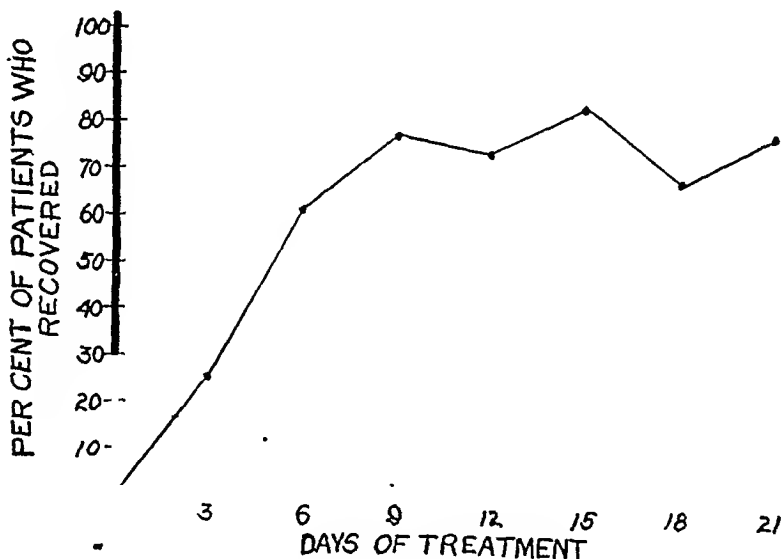


FIG. 1. Results of sulfonamide therapy in relation to the duration of therapy.

or less over a period of 30 hours or less, and another received 225,000 units daily for four days intramuscularly, plus 350,000 units intraarticularly. An additional patient who failed to recover received 225,000 units of penicillin intramuscularly for two days and 2,400,000 units of penicillin orally for the same period of time. The four other failures occurred in patients who received 2,200,000 to 21,600,000 units of penicillin for 10 to 21 days.

Of the 27 patients who received a total dose of 1,000,000 units or more, intramuscularly, 21 recovered, and of the 26 patients treated for more than five days 22 (84 per cent) responded favorably (table 5).

TABLE V  
Results of Penicillin Therapy in Gonococcal Arthritis Arranged According to the Total Dose Administered and the Duration of Therapy

Total Dose of Intramuscular Penicillin (units)	Recovered	Failed to Recover
0-1 Million	2	3
1-2 Million	4	1
2-5 Million	9	2*
5 Million and over	8	3
Total	23 (71.8%)	9
Duration (days)		
0-1	0	2
1-2	0	1
2-4	1	2
4-5		
5-10	10	1
10 and over	12	3
Total	23 (71.8%)	9

\* Includes one case treated with 550,000 units intramuscularly and 2,400,000 units orally.

Prognosis was independent of the duration of symptoms before the institution of therapy. Twenty-nine patients were classified as "acute" cases and three as "chronic." Twenty-one of the former, and two of the latter recovered (table 2).

As with the previous form of therapy, the results in the 28 patients who had no previous history of arthritis were better than in the four who had previous arthritic histories. The difference is statistically significant. Twenty-three (82.1 per cent) of the former and none (0.0 per cent) of the latter recovered.

Our experience with intraarticular penicillin is limited to two patients in whom it was given in addition to parenteral therapy, one of whom received a single injection and the other two injections. One recovered and the other failed to improve. From a review of the literature it would appear that unless the destructive process is as pronounced as in other pyogenic types the use of penicillin locally is of no added value.

*Combined Therapy.* In 23 instances the sulfonamides were combined with fever therapy. Among these, combined therapy was employed origi-

nally in 14 patients, and in the case of the others it was given after other methods had failed. As noted previously, when used alone the cabinet method of inducing hyperthermia showed a decided superiority over typhoid vaccine injection. There were no failures in 14 patients treated with the combination of sulfonamides and the Kettering hypertherm. Approximately 50 per cent of those treated with sulfonamides and typhoid vaccine failed to improve. It appears that there is no advantage to giving combined therapy initially, since the results are not significantly better than when this method is used after other forms of therapy had failed, and the rigors of such therapy are considerable.

Two patients were treated from the start with a combination of fever and penicillin. One patient with a chronic infection recovered after receiving three typhoid vaccine injections, plus 440,000 units of penicillin over a period of three days. The other patient had an acute infection and was undoubtedly treated inadequately, receiving 240,000 units of penicillin in four divided doses at four hour intervals plus three fever cabinet treatments over a period of five days. A combination of sulfadiazine and penicillin resulted in cure in one acute case.

### DISCUSSION

Three different methods of therapy are available and have received a fairly extensive trial in the treatment of gonococcal arthritis. It is important to review the results with each form of therapy so that the best method of treatment can be utilized. Prior to the development of specific therapy, the use of the available symptomatic measures was occasionally rewarded with success. In 1929, Key<sup>18</sup> stated that gonococcal arthritis is often self-limited, while, on the other hand, the affected joint seemed to be doomed regardless of any treatment employed. He further stated that joints which contain considerable excess fluid and are only moderately tender and in which there is relatively little periarticular thickening, clear spontaneously regardless of treatment.

Stecher and Solomon<sup>14</sup> were convinced that a satisfactory result was attained without medical intervention in a significant proportion of patients. Recovery followed bed rest and joint protection. Myers and his associates<sup>19</sup> reported that 25 per cent of a series of 33 patients recovered spontaneously.

On the other hand, in an analysis of 200 cases, Culp reported poor results in 34 patients whose treatment was limited to bed rest and sedation. Forty-nine patients who were given baking, diathermy, massage, prostatic massage, and passive motion failed to recover. An additional 41 patients who were treated by aspiration and the injection of air, hot compresses, manipulation under anesthesia, immobilization, incision and drainage, failed to respond.

The introduction of hypertherm treatment was a major step forward. The results with the use of the Kettering hypertherm are generally good, yielding recovery rates which ranged from 53 per cent to 90 per cent.<sup>3, 9-11, 13-15, 10, 21</sup> Most reports indicate about 75 per cent of patients recover.

Keefer<sup>9</sup> stressed that results were less striking in the chronic cases. Our findings are essentially in agreement.

On the other hand, few reports of the results of the typhoid vaccine method of therapy are variable. Culp<sup>3</sup> stated that he obtained poor results, whereas Spink and Keefer,<sup>2</sup> reported 18 recoveries out of 24 patients. It is not possible to determine the relative value of this type of treatment from a review of these reports.

Other methods of fever therapy (such as the intramuscular injection of the Corbus-Ferry filtrate, malaria inoculation and the intravenous injection of milk) have been used with varying success.<sup>3, 10, 11</sup> The disadvantages of these procedures are that they are inconstant in fever-producing properties and frequently provoke serious, uncontrollable, and occasionally fatal reactions.

The sulfonamides have a definite bacteriostatic effect upon gonococci. Spink and Keefer<sup>22</sup> showed that sulfanilamide was capable of sterilizing the synovial fluid within a short time after ingestion. Later Keefer and Rantz<sup>23</sup> pointed out that sulfanilamide diffused into the synovial fluid in about the same concentration as that of the blood, and that when the sulfanilamide concentration of the synovial fluid was maintained above five milligrams per cent the fluid was sterilized with regularity. Hench<sup>24</sup> stated that sulfanilamide was as promptly successful as fever therapy. Later other sulfonamides were shown to be as valuable.<sup>3, 9, 25-29</sup>

When the sulfonamides alone fail to cause improvement, a significant number of patients can be salvaged by combining these drugs with fever therapy. Similar results have been reported by others.<sup>13, 25</sup> Some investigators are of the opinion that the use of combined therapy has shortened the hospital stay, has produced marked and rapid relief from pain, and has restored function more rapidly.<sup>7</sup> However, the rigors of fever therapy must be considered.

Although our results show relatively good response to sulfonamides, the trend toward a decrease in efficacy of these drugs against the gonococcus appears definite<sup>30</sup> and must be seriously considered in the choice of therapy today.

Penicillin has been very successful in the treatment of gonorrhea and at present may be considered the drug of choice in the treatment of gonococcal arthritis. When adequate doses are given for a sufficient period of time, a recovery rate at least equal that produced by other methods may be expected. Moreover, since the drug is easily administered and toxic reactions, especially those of a serious nature, are so rare, it is preferable to the other methods of therapy discussed.

The duration of therapy appears to be as important as the total dose, for almost all the patients in our group who were treated for less than five days did not respond. On the other hand, 22 (84 per cent) of 26 patients recovered when treated for longer than five days.



The use of intraarticular penicillin usually is not necessary though its use has been suggested in those cases in which there has been no definite improvement with systemic penicillin alone.<sup>30</sup> A previous study by one of us showed that penicillin diffused rapidly into the joint fluid when given systemically.<sup>31</sup> Secondly, since gonococcal arthritis is not a disease of the synovial cavity, but of the synovial and periarticular tissues, the concentration of penicillin in the synovial cavity is relatively unimportant, as compared with the concentration in the tissue fluid. The four patients who gave a history of previous episodes of arthritis did not respond. The explanation may be similar to the one proposed for such diseases as mastoiditis, osteomyelitis, or endocarditis; namely, that the amount and density of the scar tissue, which has a poor blood supply, permits only partial and probably inadequate penetration of the penicillin. In these cases, still greater amounts of penicillin may effect a higher percentage of favorable responses. If penicillin in large doses is not effective, fever therapy may then be used.

#### SUMMARY AND CONCLUSIONS

1. Two hundred and two patients with gonococcal arthritis have been treated by various methods. Treatment with the Kettering hypertherm resulted in recovery in 21 (63.6 per cent) of 33 patients. Better results were obtained in patients treated during the acute stage. Typhoid vaccine was used intravenously in 22 patients. The results are not conclusive because in no case could the therapy be considered adequate.

2. Sulfonamides were used in 140 patients with favorable results in 97 (69.3 per cent) of patients. The duration of the disease did not have so great an effect upon the outcome as did the existence of previous episodes of arthritis. Only 43.1 per cent of the patients with previous attacks responded favorably, whereas 81.2 per cent without previous episodes did well. Moreover, there appeared to be a definite tendency toward a progressive decrease in the efficacy of the sulfonamides during the past few years.

3. Penicillin was given to 32 patients of whom 23 (72 per cent) recovered. Of those who were adequately treated, recovery occurred in 84 per cent. As with sulfonamides the previous episodes of arthritis had a greater bearing on the outcome than did the duration of the present symptoms.

4. Penicillin is the drug of choice in the treatment of gonococcal arthritis. It is recommended that two to five million units of penicillin administered over a period of five to ten days be used. Since sulfonamides are the simplest to administer, they may be tried first if desired, and should always be employed in those patients who do not respond to penicillin. Fever therapy is probably the most efficacious form of therapy in those patients who have a history of previous attacks of arthritis, but because of the dangers involved in such therapy it should be the last resort after penicillin and sulfonamides have failed to bring about recovery.

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# OBSERVATIONS ON PRIMARY COCCIDIOIDOMYCOSIS \*

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DURING the war years coccidioidomycosis ("Valley Fever," "Desert Fever") has received rather intensive study as the result of the concentration of armed forces personnel in the endemic areas of California and the Southwest. The present paper concerns itself with observations on 43 cases of primary coccidioidomycosis seen at the Station Hospital, Williams Air Field, Chandler, Arizona during 1946 and 1947.

Since 1935 when Dickson and Gifford<sup>1,2</sup> pointed out that infection with *Coccidioides immitis* may have a mild or primary form as well as the disseminated form originally described by Posadas<sup>3</sup> in 1892, a wealth of information has accumulated on the subject. It does not serve the purposes of this paper, however, to attempt a review of these writings or to give more than a brief background of the etiology and pathogenesis of the disease.

The causative agent of coccidioidomycosis is the fungus *Coccidioides immitis*. The fungus exists in two stages: The saprophytic stage ends in the formation of the chlamydospore which is the infective stage for man. The parasitic stage which is seen only in animal tissues, sputum, or exudate is recognized as a doubly refractile spherule containing endospores. The infective chlamydospore is most often inspired with dust, although rarely it may enter the body through the skin. The fungus has a particular affinity for the respiratory tract, however, and only a negligible number of infections have their origin elsewhere.

Emmons<sup>4</sup> feels that the disease is primarily a disease of rodents, which is transmitted to man only through accidental contact with dust previously contaminated with spores from infested rodents.

Smith<sup>5</sup> has classified infections with *C. immitis* in the following useful and distinct manner:

1. Initial or primary infection (self limited, nearly always respiratory).
  - a. Asymptomatic form (commonest form which involves most residents of the endemic sections).
  - b. Acute respiratory, influenzal, or pneumonic form.
  - c. Either of the above types associated with erythema nodosum or erythema multiforme.
  - d. Pulmonary cavity form (probably a complication of b).

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2. Progressive disseminated form (coccidioidal granuloma). Our discussion will be concerned entirely with the initial or primary infection described above.

### MATERIAL, PROCEDURE, AND METHODS

We have studied 43 cases of considered proved coccidioidomycosis. The patients' ages varied from 18 to 35 years. There were 39 males and four females. Of the 39 males, there were seven Negroes and one Filipino. There were no deaths in the series.

Although it has been stated that recent entry into an endemic area, positive coccidioidin skin test, and elevated sedimentation rate are sufficient to make the diagnosis,<sup>6</sup> we have included only those cases which could definitely be established as coccidioidal by laboratory confirmation. In most cases we have used the complement fixation and precipitin serological tests as performed through the courtesy of Dr. Charles E. Smith, Stanford University, to establish the diagnosis. In two cases, demonstration of the fungus in the sputum has been confirmatory.

In each case we have noted the length of time in the endemic area, relative degree of exposure to dust, symptoms, physical findings, results of skin testing with coccidioidin, sedimentation rate, chest roentgenograms, serological tests, length of hospitalization, and follow-up progress.

The coccidioidin for skin testing was supplied by Dr. C. E. Smith. Unless otherwise noted, this was used in a dilution of 1:1000, prepared from undiluted material once a month.

Five of the patients were transferred to Army General Hospitals for further observation and care because of the fear of dissemination. The remainder were all followed at the Station Hospital, Williams Field, Arizona.

### RESULTS

*Length in Endemic Area.* The shortest time any individual had been in the area was one month; the longest was 19 months. The average of all cases was six and one-half months.

*Dust Exposure.* This was rated on the basis of 1 to 4 +. No particular exposure was rated as 1 +, moderate chronic exposure such as working on outside details as 2 +, severe chronic exposure (working in motor pool or airplane flight line) as 3 +, and a heavy exposure definitely recalled by the patient as having occurred within three weeks of the onset of illness as 4 +.

Fifteen were rated as 1 +; seven were rated 2 +; six were rated 3 +; and nine as 4 +. The remainder were not rated.

*Symptoms.* 1. Chest pain was by far the most common symptom. Thirty-nine of the patients (90 per cent) complained of pain, characteristically aggravated by respiration or coughing. In most cases the pain was substernal and poorly localized. It was most often described as "right in the middle," or "under the breastbone."

It is noteworthy that this pain which may be severe at the time of admission almost always subsides within one or two days of hospitalization. It was the unusual case which persisted in having pain longer than 48 hours.

2. Cough was a complaint in 19 of the cases (44 per cent). This was most often nonproductive in nature and disappeared within several days of hospitalization.

3. Malaise was a prominent symptom in 14 cases (32 per cent). Although it was mentioned specifically by only 32 per cent, nearly every patient on questioning was willing to admit fatigue and general sense of ill being. In most cases this symptom was found to persist for a longer period of time than any other symptom.

4. Fever and chills were symptoms in 13 cases (30 per cent). The fever in most cases was low grade and, similar to the chest pain and cough, disappeared within the first two or three days of hospitalization. The highest temperature at time of admission was 103°.

5. Headache, usually generalized, was complained of by 12 patients (28 per cent).

6. Substernal pain on swallowing was a feature in 11 of our patients (25 per cent). Although it was noted by only one in four, we have observed that when present it is one of the most characteristic symptoms of primary coccidioidomycosis, and its existence is extremely suggestive of the disease.

The discomfort is usually beneath the upper sternum, and at times may be of sufficient severity that the patient will refuse solid food and limit himself to liquids.

7. Mild sore throat was a feature in six cases (14 per cent).

8. There were two patients who were admitted with hemoptysis. In both cases the sputum was only blood streaked and was small in amount.

9. Two patients complained of right upper abdominal pain and are further described under physical findings.

*Skin Manifestations.* A total of 14 per cent of the patients exhibited allergic skin lesions. Four patients (9 per cent) had erythema nodosum, limited to the pretibial surface of both legs. Two patients (5 per cent) had erythema multiforme distributed over thighs, buttocks, and sacral region.

*Physical Findings.* The physical findings were so inconstant, and when present were of such questionable accuracy as to make statistical figures of no value. It is interesting to note that two patients were admitted with severe right upper abdominal pain and sufficient muscle guarding to justify the admitting diagnosis of gall-bladder colic. Both of these were discovered to have pulmonary infiltration above the right diaphragm.

*Coccidioidin Skin Testing.* The skin test was carried out on all patients. 0.1 c.c. of 1:1000 Coccidioidin was injected intracutaneously in the forearm and read at 48 hours. The reaction was read as 1 to 4+, using the following criteria of Cheney and Denenholz<sup>7</sup>:

- 1 + Induration and erythema 0.5 to 1 cm.
- 2 + Induration and erythema 1 to 2 cm.
- 3 + Induration and erythema greater than 2 cm.
- 4 + Vesiculation in addition to erythema and induration.

Fifteen were read 1 +, 16 as 2 +, nine as 3 +, and two as 4 +. One patient was initially negative in the 1:1000 dilution but was found to be strongly positive with the 1:100 dilution.

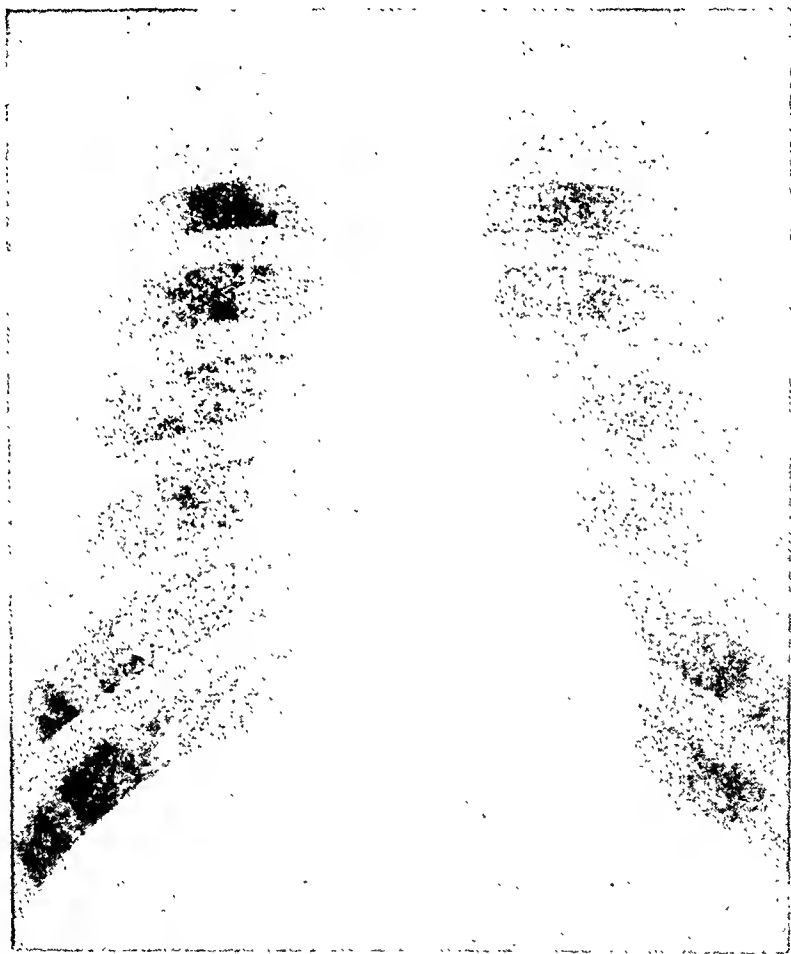


FIG. 1. Lobular infiltration and thickened hilar markings on the left in an 18 year old white male who had been in Arizona for one month. Hospitalized following four days of substernal pain and malaise. Coccidioidin skin test 3 plus and sedimentation rate 21 mm. per hour. Total hospitalization 25 days. Film five months later revealed persistent nodular remnant of previous infiltration, although patient was asymptomatic and sedimentation rate normal. Serological confirmation was obtained.

*Sedimentation Rate.* Sedimentation rates (Wintrobe tube method) were done on admission and repeated at weekly intervals until normal. Elevation above the normal was found in every case. The highest initial rate in our series was 51 mm. per hour (uncorrected). The average rate on admission was 32 mm. per hour (uncorrected).

*Chest Roentgenograms.* All but one of our cases presented abnormal findings on roentgen examination of the chest. The types of involvement seen included (1) diffuse pneumonia-like infiltrations, (2) hilar thickening, (3) hilar and mediastinal adenopathy, (4) nodular parenchymal lesions, (5) cavitation, and (6) effusion. None of our cases exhibited bony involvement of the chest cage. In evaluating and classifying this series of films we were aided by previous reports on the roentgen findings of coccidioidomycosis.<sup>6, 8, 9</sup>



FIG. 2. Bronchopneumonic-like infiltration and moderate hilar thickening on the right in an 18 year old white male who had been in Arizona for one year. Hospitalized after five days of malaise and substernal pain, and two days of erythematous rash on arms and trunk (erythema multiforme). Coccidioidin skin test 2 plus, and sedimentation rate .27 mm. per hour. Serological confirmation was obtained. Hospitalized for 12 days.

1. *Pneumonia-Like Infiltrations.* These were by far the most common radiologic findings, being present in 35 cases (83 per cent). The majority of these (21 cases) were isolated, peripheral, lobular infiltrations which were well circumscribed and of homogeneous density (figure 1). Ten of these infiltrations involved the lower lobes, and 10 the basal portions of upper lobes. In one case the involvement was apical and closely resembled active reinfection tuberculosis. Abnormally thickened hilar shadows are a frequent accompaniment of this type of infiltration, and less frequently true hilar adenopathy has been noted. Complete resolution of the peripheral infiltrations



occurred within five days to three months (average 20 days) in 11 of these cases. Resolution in the others was incomplete in from one to 10 months, and characteristically left a discrete fibrous nodule at the site of the infiltration. Cavitation subsequently occurred in two of these nodules.

The other 14 cases of pneumonia-like infiltration were fan-shaped in type and radiated from the hilar region outward into a lung field (figure 2). They most resembled primary atypical pneumonitis. Eight of these infiltrations involved lower lobes (one bilaterally), three involved the basal portion of an upper lobe, and three were situated in the apex of an upper lobe.

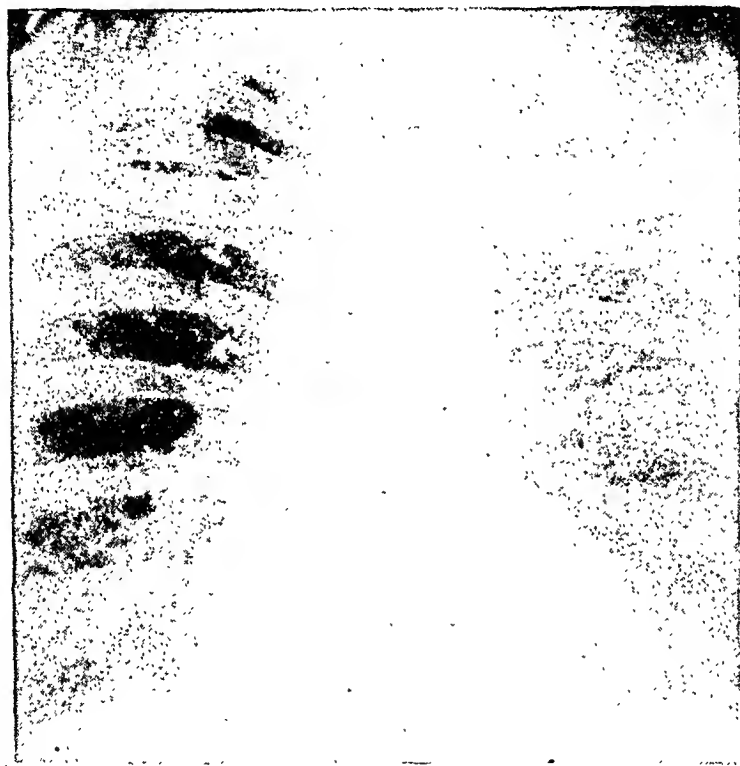


FIG. 3. Marked mediastinal widening, slight left hilar thickening and adenopathy, and fan-shaped left apical infiltration in a 27 year old negro male who had been in Arizona for three months. Two week history of cough and dull pain in left upper chest. Coccidioidin skin test 3 plus, and sedimentation rate 50 mm. Serological confirmation obtained. Sedimentation rate still elevated after one month.

All three of the apical cases simulated active reinfection tuberculosis. Co-existent thickened hilar markings were frequent, and somewhat less frequently hilar and mediastinal adenopathy, and basal effusion was present. Complete resolution occurred in five days to three months (average one month) in seven cases, and in the remaining seven cases incomplete resolution in one to 10 months. This last group included four of the patients who were transferred to General Hospitals because of the fear of dissemination.

2. Hilar Thickening. This was noted in 28 cases (66 per cent), and consisted of soft peribronchial infiltration which produced fuzzy, widened

bronchovascular markings, often difficult to evaluate. In six of our cases this constituted the only roentgen finding, although the remaining 22 had associated peripheral infiltration, as mentioned above. Slow resolution (three weeks to seven months) was a feature of those which showed only thickening.

3. Hilar and Mediastinal Adenopathy. These findings were noted in 19 cases (45 per cent) (figure 3). Twelve showed hilar adenopathy alone, and seven exhibited both hilar and mediastinal adenopathy. The association of adenopathy with parenchymal infiltration has been mentioned previously. Resolution occurred in periods which varied from seven days to nine months, and was noted to be much more rapid when the mediastinal glands were not involved. Those with both hilar and mediastinal adenopathy resolved very slowly.

4. Nodular Parenchymal Lesions. Although discrete fibrous nodules have been said to represent the most characteristic and diagnostically specific finding in primary coccidioidomycosis, we noted that when present they represented incomplete resolution of a previous coccidioidal infiltration, usually of the lobular type. Serial films showed nodule development from a previous infiltration in six cases over periods of time which averaged 5 months. The nodules averaged 2 cm. in diameter, were single, isolated, well circumscribed, and showed no evidence of calcification. They were equally distributed between the upper and lower lobes.

5. Cavitation. Two of the nodules mentioned above progressed to cavitation, the first undergoing transformation from a lobular infiltration to a discrete nodule to cavity in 11 days. The other cavitation occurred slowly over a period of eight months. These cavities remained practically static for periods of five to 10 months, and were further characterized by lack of inflammatory change in the surrounding area, a moderately thin wall, and upper lobe involvement (figure 4).

6. Pleural Effusion. This was noted in three cases and was associated in all three with parenchymal infiltrations. Effusion was minimal in the right costophrenic sulcus and along the right lesser fissure in two cases, but was massive in the third and obscured the entire left lower lobe (figure 5). The minimal effusions cleared within three days, while the massive effusion cleared in 21 days.

*Serological Tests.* Through the courtesy of Dr. Charles Smith, Stanford University, complement fixation and precipitin determinations were made on nearly all of our cases. We have used this service almost entirely to confirm the diagnosis, rather than to follow the progress of the disease. It would have been desirable to have repeated studies on each case especially as a check on the possibility of dissemination, but due to the time and distance involved we have limited ourselves to one determination, usually performed between three or four weeks after the onset of symptoms.

*Treatment.* Treatment in every case consisted of bed rest until chest films and sedimentation rates were improved, and sharply limited activity in the hospital until the sedimentation rate was normal and chest films were either clear or static for at least one week. Symptomatic therapy such as salicylates and cough mixtures were used as necessary. Chemotherapy was not attempted.

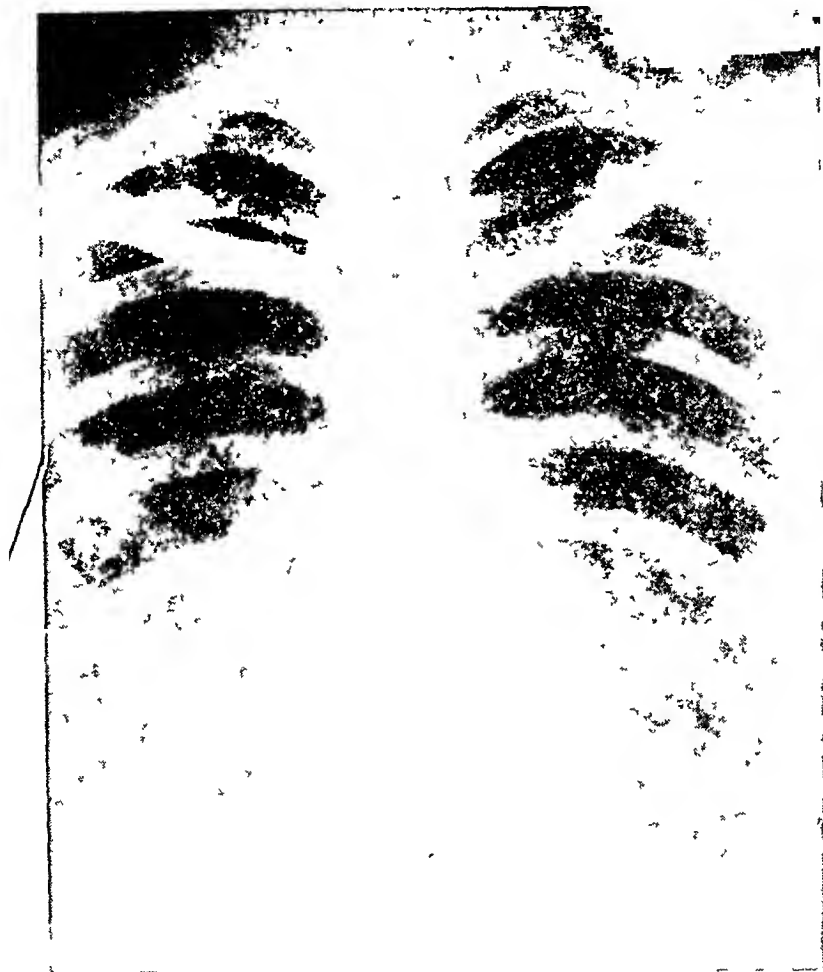


FIG. 4. Discrete cavity in the right mid-lung field with moderate right hilar thickening in a 15 year old white female who had been in Arizona for one year. Initial lesion was lobular infiltration in the same area one month previously. Coccidioidin skin test 3 plus, sedimentation rate 37 mm. per hour. One month later this lesion regressed to a nodule, and five months later appeared unchanged. Serological confirmation was obtained.

*Length of Hospitalization.* The average length of hospitalization at this station was 21 days. The longest hospital stay was 42 days, and the shortest was 10 days. For the six patients transferred to a General Hospital, the average length of hospitalization was 120 days, although none of the cases was found to exhibit the disseminated stage. The hospital stay of the negro patients averaged six days more than the white patients.

*Follow-Up of Cases.* We have been able to follow 22 of our cases by personal interview for periods varying from two months to one year. All but two patients stated that they had no symptoms and felt "as good as ever" at the time of interview. However, nearly all admitted having fatigue for the first few days following discharge from the hospital.

Both of the patients who claimed sequelae described vague chest pains on exertion and stated that they still felt tired and weak after five months. Radiologic studies of the chest and sedimentation rates were repeated and found normal.

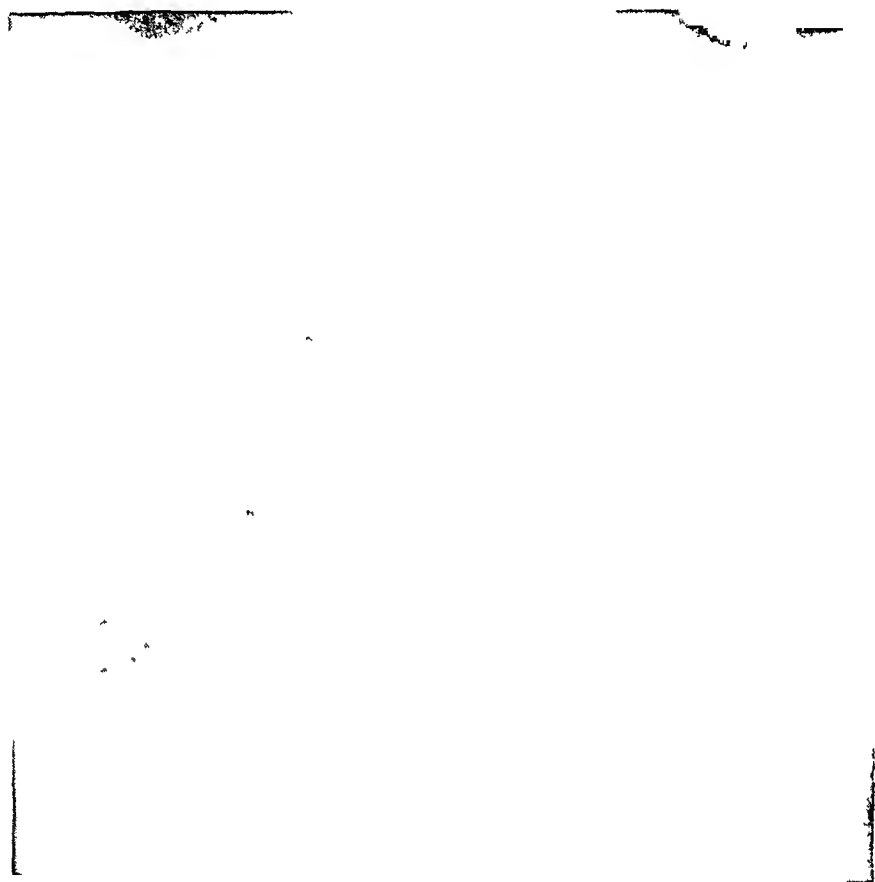


FIG. 5. Massive left pleural effusion and moderate right hilar adenopathy in a 26 year old Filipino male who had been in Arizona for four months. Hospitalized following two days of severe left chest pain and cough. Coccidioidin skin test 2 plus and sedimentation rate 23 mm. per hour. *Coccidioides immitis* demonstrated in sputum, and serological confirmation obtained. Effusion completely cleared in less than one month.

*Incidence of Positive Kahn Tests.* Routine Kahn tests were performed on each patient using the Standard Kahn accepted by the U. S. Army.

Three of these were returned as positive. The first was in a 19 year old negro male who denied any history of syphilitic infection, malaria, or yaws. The test was repeated and again returned as positive. Since it is our policy to check our own positives with quantitative Kahns and Wassermanns performed in the 6th Army Laboratory, San Francisco, a sample of serum was

forwarded for confirmation. Unfortunately this was apparently lost in transit. Another Kahn was performed in our laboratory two weeks later and reported as doubtful. Five weeks after the initial positive reports, another specimen was found negative and continued negative on two subsequent examinations at monthly intervals.

The second case was a 28 year old white male who similarly denied history of infection. The initial Kahn performed in our laboratory was positive. This was confirmed by a 6th Army report of 20 Kahn units although the Wassermann was negative. After five weeks, the Kahn became doubtful, and at six weeks turned negative. This was confirmed by another negative specimen taken one month later.

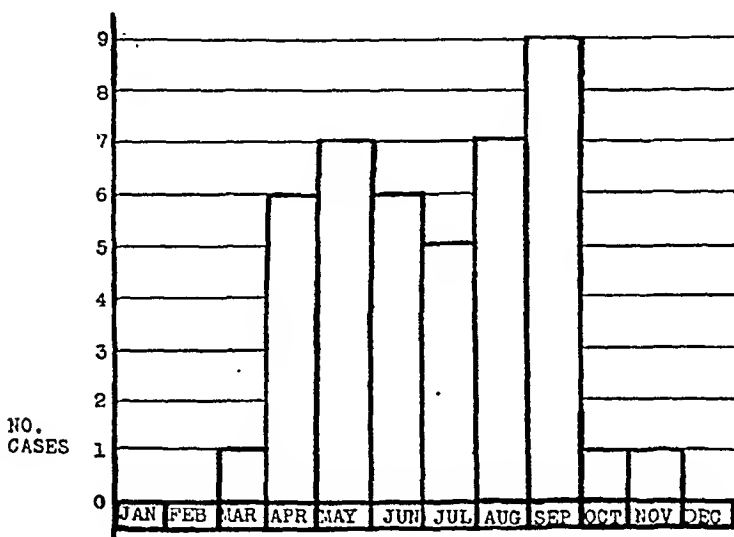


CHART 1. Incidence of coccidioidomycosis according to months.

The third case was a 20 year old Negro male who had been treated for latent syphilis at the induction station 15 months previously, using combined penicillin and heavy metal therapy. He had been followed in our Venereal Disease Clinic at monthly intervals and had had four negative Kahns during that time. Following hospitalization for coccidioidal infection, the Kahn was reported positive and continued positive for two months, at which time he was transferred to another station.

*Seasonal Incidence.* (See chart 1.)

## DISCUSSION

One general fact which has impressed us in observing coccidioidomycosis over two seasons has been the relative well being and comfort of the patient once he has been in the hospital for one or two days. Despite markedly elevated sedimentation rates, extensive pulmonary infiltration, and even fever, the patient will state that he feels well and would like to be up and about. Our greatest problem has been to make the patient appreciate the

necessity of bed rest in the absence of symptoms. For this reason each patient is told at the time of admission something of the nature of his illness, the reason for adequate rest, and the approximate length of time he will be hospitalized.

We have also confirmed the fact that the Negro, in general, exhibits more severe symptoms than the white, is more susceptible to the disease, and has a longer convalescent period.

Dysphagia, or pain on swallowing, as mentioned previously, has been of value to us many times in differentiating coccidioidomycosis from the more common simple respiratory infections. We feel that this is best explained by an extensive hilar adenitis or low grade mediastinitis, and perhaps an esophagitis, but we have been unable to make any particular investigation to substantiate this belief. Undoubtedly we have placed more reliance on dysphagia than is warranted for any one symptom as a diagnostic point, but as a general rule we believe that it is safe to state that any patient in an endemic area with predominantly respiratory complaints associated with substernal pain on swallowing should be considered as coccidioidomycosis and properly investigated.

Assuredly, coccidioidal infection is potentially a fatal disease if dissemination occurs. The primary form, however, has appeared extremely mild, and with laboratory facilities to aid in suggesting the danger of dissemination, we do not believe it necessary to hospitalize these patients for longer periods than we have in our present series. Such follow-up studies as we have been able to carry out have substantiated this belief. We would emphasize, however, that each case must be treated according to its individual merits.

The significance of the positive Kahn test in two individuals, previously negative, and in one case previously treated but with subsequent negative reports, is questionable. Sweigert, Turner and Gillespie<sup>10</sup> report on four positive Kahns incidental to coccidioidal injection in their series of cases. We can merely confirm that this has occurred in our series as well, and mention it as an interesting finding which deserves further investigation.

Although we feel certain that we have seen at least 75 cases of coccidioidal infection, we have reported on only those which we felt were definitely confirmed. This, perhaps, accounts for the unusually high percentage of allergic skin manifestations in our series, as compared to the 2 to 5 per cent established by Smith.<sup>5</sup>

Coccidioidomycosis still remains a problem primarily for the physician of the endemic areas. To the physician elsewhere it undoubtedly will continue to have little significance as a primary concern in medical diagnosis. However, Kurz and Loud<sup>11</sup> have recently reported from New England the importance of the disease in interpreting chest films in individuals who have at any time resided in the endemic areas. Kundstadter and Pendergrass<sup>12</sup> have emphasized the possible pediatric problem which may arise in confusing childhood tuberculosis with acute, subacute, or healed coccidioidal infection. Clark and Gilmore<sup>13</sup> have also stressed the similarity in radiologic ap-

pearance of tuberculosis and persistent or slowly disappearing coccidioidomycosis and urge careful investigation.

We are of the opinion that coccidioidomycosis deserves a place in the differential diagnosis of any acute or chronic pulmonary infection for which an immediate cause is not apparent. Similarly, we feel that when abnormal shadows are noted on routine radiologic examination of the chest in any individual with a history of residence in an endemic area, the disease warrants consideration.

### SUMMARY

1. Observations on 43 cases of primary coccidioidomycosis are presented. These observations concern themselves with length and severity of exposure, symptoms, physical and laboratory findings, and subsequent follow-up studies.

2. The roentgen findings are classified and described according to types, and the frequency of incomplete resolution is mentioned.

3. The occurrence of dysphagia as an important diagnostic help is described.

4. Three cases in which positive Kahn tests developed incidental to coccidioidal infection are described.

5. The relative mildness of the disease and early symptomatic recovery of the patient are discussed.

6. Some knowledge of the nature of the disease is recommended for physicians both in and out of the endemic areas.

Photographic reproductions by Cpl. T. M. Roberts, Base Photo Laboratory.

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# CASE REPORTS

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## ACUTE PORPHYRIA: REPORT OF TWO CASES WITH ELECTRICAL STUDIES IN ONE \*

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PORPHYRIA, although an uncommon disease, has been well described by such investigators as Günther,<sup>1</sup> Mason, Courville and Ziskind,<sup>2</sup> Watson,<sup>3-5</sup> Turner,<sup>6</sup> Waldenström,<sup>7, 8</sup> Dobriner and Rhodes,<sup>9</sup> Nesbitt<sup>10</sup> and Watkins,<sup>11</sup> and Welcker.<sup>12</sup> Oddly enough few medical textbooks discuss this interesting metabolic disease adequately or at all. However, as more cases are being reported the disease is becoming more generally known. Its early recognition would prevent unnecessary operative procedures and administration of contraindicated drugs, as well as lessen confusion with certain neuropsychiatric disorders.

There are two main types of porphyria, acute and congenital. They are considered to be due to an inborn error of metabolism but little is known regarding this metabolism. Acute porphyria has been classified as toxic or idiopathic depending on whether a causative agent is found.

The purpose of this paper is to report two additional cases of the acute idiopathic type. One patient had neurologic complications with residual symptoms, the other had none. Electrodiagnostic studies were done on the former, with the help of an electromyograph and a constant current impulse stimulator.<sup>13, 14</sup> The latter was devised by Golseth and Fizzell.<sup>15</sup> Dillon<sup>16</sup> has recently reported the use of this type of electrical test on peripheral nerve injuries and the interpretation of tetanus ratio, chronaxie, repelitive stimuli, strength duration curve in normal, regenerating, degenerating, and denervated states. The literature reveals few studies on electrical excitability of muscles in porphyria, and only one previous report so far as could be determined with the use of the electromyograph.<sup>17</sup> It was thought that such studies might be of some value in light of the postmortem findings reported by other investigators in cases of acute porphyria.

There seems to be no doubt that some product of the porphyrin metabolism can produce damage to the nervous tissue since involvement of peripheral nerves is seen so frequently. However in some cases of porphyria the nervous system is not involved. The presence of porphyrins in the sympathetic ganglia has been considered to be the cause of abdominal distress.<sup>2</sup> Porphyrins have been found in other tissues of the body, including the central nervous system and liver.<sup>2, 18-20</sup> This paper is concerned chiefly with the effect on peripheral nerves.

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Ross and Bury,<sup>21</sup> in 1893, noted that in porphyria with Landry's type of paralysis the electrical excitability of paralyzed muscles frequently remained unaltered. Grünwald,<sup>22</sup> in 1922, noted electrical reactions like those of myasthenia gravis in a case of porphyria with paralysis. Mason, Courville, and Ziskind<sup>2</sup> reported widespread and patchy degeneration of the myelin sheaths and axis cylinders in motor nerves. Palmer<sup>18</sup> reported a case of acute idiopathic porphyria with acute ascending paralysis. At necropsy he found marked degenerative changes in the liver and kidney, and in the myelin sheaths of the peripheral nerves. In certain parts of the nerves lymphocytic infiltration was present. Prior to death the patient had had bilateral ankle and wrist drop and ptosis of the left eyelid.

Baker and Watson<sup>19</sup> also described extensive changes in the peripheral nerves, chiefly in the median nerves, in the form of demyelination and vacuolization. The most advanced changes were observed within the center of the nerve with the periphery keeping somewhat its normal architecture. In many regions the myelin sheaths were completely disrupted, leaving only faint outlines of globules as a residual of the destroyed tissue. The axones showed a wide range from swelling and color loss to a marked fragmentation and total disappearance. In the cervical anterior horn cells chromatolysis, swelling and neurologic changes were observed. Muscle fibers appeared to have lost their striations, normal staining properties, and there was a partial disappearance of the sarcolemma. Complete muscle degeneration was not observed, even though the patient had had the disease and had been under observation for about three years. Denny-Brown and Sciarra<sup>20</sup> in 1945 also recorded pathologic changes practically identical with those of Baker and Watson.

In a case reported in the *New England Journal of Medicine*,<sup>17</sup> quadriplegia developed and death from respiratory paralysis occurred 19 days later. At necropsy marked degenerative changes were found to have affected a large proportion of the nerve fibers. The myelin sheaths were swollen, constricted, incompletely divided into short segments, and in many instances broken up into round fragments. There were many fusiform enlargements and constrictions of the axis cylinders. The spinal cord showed axonal reactions of the anterior horn cells; namely, swelling of the cells and central chromatolysis of the Nissl substance. An electromyogram done on the fourth hospital day showed a low voltage, repetitive discharge in the left and right extensor carpi radialis, as well as in the left gastrocnemius muscle.

Muscular atrophy has been seen frequently as a sequel to porphyria. It is of interest to note the atrophy reported recently in the case of Halpern and Copsey<sup>23</sup> and DiFiore.<sup>24</sup>

Yeager<sup>25</sup> has recently presented a close diagnostic differentiation between the neuritis of porphyria and of Guillain-Barré syndrome; he emphasized the involvement of motor nerves and poor prognosis in the former in contrast to motor and sensory nerve involvement and fairly good prognosis in the latter. This disease is emphasized in differential diagnosis because it is not infrequently confused with acute porphyria as illustrated in my second case. In one of Hoagland's<sup>26</sup> cases of acute porphyria Guillain-Barré syndrome was suspected at first.

## CASE REPORTS

*Case 1.* The patient was admitted to Ashford General Hospital, White Sulphur Springs, on February 24, 1946. He was 30 years of age, unmarried and a veteran of World War II, who had been discharged January 28, 1946. He had entered the service in January, 1942, and while in the Army had visited the dispensary only four times because he had difficulty in holding his urine while sitting in lectures or shows. Nothing abnormal was ever found in the urine, and during those four years he had never been hospitalized.

On admission, the patient complained of pain in the abdomen and back, aching in the arms and legs and much fatigue. He stated that on February 20, 1946, he had shoveled about six tons of coal from a truck into a basement, and on the following day he awoke early with severe abdominal pain. Two days later he had not improved in spite of treatment at home; the abdominal and back pain continued, and he felt feverish for the first time. Hospitalization was advised. He vomited twice on this day, had frequency of urination, about 15 to 20 times, which lasted one day. There was no dysuria and no abnormal color of the urine.

The family history was negative. The past personal history was also non-contributory. He had had measles, mumps and chickenpox.

On examination in the hospital the patient was moderately apprehensive and nervous and did not appear acutely ill. He was 5 feet 11.5 inches tall (182 cm.) and weighed 145 pounds (65.8 kg.). There was telangiectasis on both cheeks. The gums bled easily. The pulse while he was sitting was 108 beats per minute and blood pressure in millimeters of mercury was 160 systolic and 90 diastolic. Tachycardia was noted. The liver and spleen were not palpable. The muscle tone and the grip in both hands and strength of the muscles of the lower extremities and the neck were good. Generalized tenderness was elicited throughout the abdomen. On examination of the genitalia pink stains were found on the patient's underclothing. The patient stated he had never observed similar stains before. A specimen of urine was obtained, and it was found to be pink, which turned to a darker red on exposure to light. A test for porphyrins gave positive results, and a provisional diagnosis of acute porphyria was made, after the fifth day of hospitalization. During the first four days in the hospital a presumptive diagnosis of ulcer was made because of blood-tinged vomitus. Treatment consisted of a bland diet and antispasmodic drugs, codeine sulfate, phenobarbital, and pentobarbital sodium until the diagnosis was established.

Tests revealed the urine to contain coproporphyrin and uroporphyrin, the latter in the amount of 0.4 mg. per 100 c.c. of urine. A positive test was obtained for porphobilinogen. The patient's temperature rose to 102° F., but fell to 99.2° on February 25, 1946. On February 26 erythrocytes numbered 4,130,000 per cubic millimeter of blood, a sedimentation rate on two occasions was 3 and 11 mm. for the first hour, and the hematocrit reading was 40 and 42 on two occasions also. Serial electrocardiograms revealed a broadening of and dome-shaped T-waves with a prolonged Q-T interval at the height of illness. It was the opinion of the cardiovascular consultant that the patient had an acute hypertension secondary to the acute porphyria. He also noted a violaceous discoloration of the exposed and acral portions of the ears, elbows, shoulders and malleoli. Examination of the eye revealed normal ocular fundi. Neurologic examination was negative, no abnormal reflexes being present. The abdominal reflexes were hyperreactive, and there was no muscular paralysis or atrophy. Cystometric examination revealed evidence that the capacity of the bladder was normal. Proctoscopic examination was negative. Roentgenograms of the lumbosacral portion of the spinal column, of the upper part of the gastrointestinal tract and the colon and the chest were all negative.

This patient made a fairly rapid recovery and was dismissed from the hospital

in six to eight weeks. No electrical tests were performed since there were no neurologic complications.

*Case.2.* This patient, an army nurse 25 years old, who had seen two years of service was admitted to Percy Jones General Hospital on November 22, 1946 because of Guillain-Barré syndrome. On the trip to the Southwest Pacific theater in 1945 she sustained a severe sunburn on one occasion. Later an upper respiratory infection developed and continued for about a month. This was followed by weakness, anorexia, malaise and an aching of the midabdominal region, with severe lancinating pains around the lumbar region, which later progressed down both legs. Sweating increased in the lumbar region and progressive weakness was noted in the right arm, forearm and hand. The patient was hospitalized on October 3 for 17 days. Her condition was considered an anxiety reaction, and she was told she would be all right as soon as she became accustomed to army life. She asked to go back to duty to avoid the neuropsychiatric consultant with whom she disagreed, even though muscular weakness had begun in her upper extremities and both thighs and hips felt numb. Saddle anesthesia was present for seven to 10 days. She could feel pressure, but no pain. Before her dismissal she was unable to raise her right arm above her head.

Four days after her return to duty she was admitted to another hospital in the Philippine Islands because she was unable to do such simple things as manipulate a hypodermic syringe and was weak and trembling after any activity. Blood pressure was 120 mm. of mercury systolic and 95 diastolic. The pulse rate varied from 124 to 84, with an average of about 90 beats per minute. Her deep reflexes were active and equal; the superficial reflexes were normal. Neurologic examination revealed 75 per cent paralysis of the left deltoid muscle, 100 per cent paralysis of the right deltoid muscle, 25 per cent weakness of the pectoral muscles and 75 per cent weakness of the biceps muscles bilaterally. About 25 per cent atrophy was noted in the muscles of the right shoulder girdle. She had some difficulty in swallowing and breathing in the initial stages of the disease. A diagnosis of infectious neuronitis of the fifth and sixth cervical segments was made. About November 1 facial palsy developed. The patient was transferred by air to the United States on November 10, 1945.

In the States quadriplegia was noted. She could not walk or use her upper extremities. She could not sit up without assistance, or wrinkle her forehead, and her facial expression was flat on the right side. Her ability to cough and speak was considerably impaired. She complained of severe pain in her extremities. She was unable to close her eyes completely. The abdominal reflexes were intact. All reflexes in the upper extremities were absent. No sensory changes were noted. Function returned to the lower extremities fairly rapidly, but the knee reflexes were absent. The ankle jerks were present and active. On November 22, 1945, her blood pressure was 130 systolic and 94 diastolic. Her pulse rate was 100. About December 10 she began to walk with assistance and by December 28 she was able to lift her hands. All laboratory tests, including analysis of spinal fluid, gave negative results except for a slight diminution in erythrocytes and hemoglobin in the blood. The diagnosis of infectious neuronitis or Guillain-Barré syndrome was concurred in.

Between February 26 and November, 1946, when she entered the Percy Jones General Hospital this patient was admitted to four additional hospitals with the diagnosis of Guillain-Barré syndrome. Spinal fluid was essentially normal on two occasions except for an elevation of protein to 58 mg. per 100 c.c. at one time. Her condition gradually improved, but three exacerbations, in the spring, summer and fall, interrupted the steady progress. The exacerbations were characterized by part or sometimes by all of the following symptoms: slight fever; anorexia; weakness; loss of weight; occasional nausea and vomiting; generalized abdominal tenderness; girdle-like abdominal pain; pain in the lower extremities; tachycardia and hypertension.

Usually there was a prodromal period of malaise and vague complaints which the patient referred to as "a cold." At one hospital, which she entered because of a "cold" and fear of another recurrent attack, analysis of urine disclosed a dark red-amber color. During the second exacerbation opiates had to be used to control severe muscular aches. Use of these was continued off and on until December, 1946. In October, 1946, the patient's mother, who apparently had had hypertension for some time, died from a cerebrovascular accident.

At the time of admission to the Percy Jones General Hospital the patient was having her second episode of saddle anesthesia which lasted about 10 days. Her complaints were severe aching and weakness of the upper and lower extremities, and especially about the shoulders, arms and hands.

The family history was not significant. The patient had had the usual childhood diseases, influenza and five years previously an appendectomy. She stated that the pain in her attack of appendicitis was a little unusual because it was located on both sides of her abdomen and extended downward in a V formation. No exposure to toxic agents was found. Her menstrual periods had been irregular and amenorrhea had existed since October, 1946.

Physical examination on admission revealed marked weakness and atrophy of the muscles of the shoulder girdles, arms, forearms and hands, more marked on the right than on the left, a pronounced weakness and clumsiness in the use of her hands with practically useless thumbs and atrophy of the muscles of the back. The legs appeared normal. Many muscle groups were tender and aching. A slight facial weakness was noted. The deep reflexes were equal and within normal limits bilaterally. No sensory disturbance other than hyperesthesia about the arms was noted. Her blood pressure was 108 mm. systolic and 78 diastolic. The heart rate was normal. The liver and spleen could not be palpated.

On January 4, 1947, further examination was carried out. At this time the patient did not appear acutely ill and weighed 105 pounds (47.6 kg.). Obvious atrophy of the muscles of the shoulder girdles and of the upper extremities, a residual of her former facial paralysis and a lid lag on the left were present. No nystagmus was noted. The gag reflex was present and hyperactive. No impairment of sensation was found. Babinski's and Romberg's signs were negative. The knee jerks were diminished, while the ankle jerks were lively and equal bilaterally. Abdominal reflexes were present in the upper quadrants. The biceps tendon reflexes were diminished, and the triceps tendon reflexes were not elicited. Both upper extremities were weak; the right was the weaker. The patient was able to abduct the left shoulder to 90 degrees, the right only about 20 degrees. She was hardly able to flex the right elbow enough to get the right hand to her mouth. As a matter of fact, she was just barely able to overcome gravity and flex the elbow from 180 to 45 degrees. The patient found it difficult to get up from a supine position. She managed it, by turning on her right side, and using her left upper extremity to push herself up to a sitting position. Her teeth were definitely discolored and contrasted markedly with two false teeth which had matched the other teeth perfectly in color two years previously.

About six weeks later the patient was able to abduct and elevate her upper extremities as shown in figure 1. Her hands, however, failed to show improvement (figure 2). She was unable to dress or put up her hair. The strength of the lower extremities was found to be within normal limits and equal bilaterally.

Laboratory tests in January, 1947: Erythrocytes numbered 5,170,000 and leukocytes 12,000 per cubic millimeter of blood. There was 14.0 gm. of hemoglobin per 100 c.c. of blood. A differential count showed 61 per cent neutrophils, 3 per cent eosinophils, 2 per cent basophils, 9 per cent monocytes, and 25 per cent lymphocytes. The Kahn test was negative for syphilis. The urine was a pale amber



FIG. 1. (case 2). Atrophy and weakness in shoulder girdle muscles with muscle substitution and resultant cervicodorsal scoliosis. (Picture was taken in recovery phase.)

color and contained three to five leukocytes and 12 squamous epithelial cells per high-power field. Its specific gravity was 1.005.

Tests of the blood showed concentrations of 4.3 mg. of phosphorus and 9.4 mg. of calcium per 100 c.c. of serum, 20 mg. of urea, 1.7 mg. of creatinine, 83 mg. of sugar per 100 c.c. of blood and 480 mg. of chlorides and 240 mg. of cholesterol per 100 c.c. of plasma. Her basal metabolic rate was  $-9$  per cent. Cephalin flocculation and bromsulfalein tests of liver function gave negative results. Analysis of spinal fluid showed no cells, a negative Wassermann reaction, a gold curve of



FIG 2 (case 2). Patient's hands on left. A normal hand on right. Atrophy of muscles of the thenar eminences of patient's hands, especially of the patient's left hand. Both thumbs of patient demonstrate marked atrophy and loss of strength by their extreme lateral and flat position. Contrast with normal hand on extreme right.

0000000000, and a total protein of 50 mg. per 100 c.c. with a faint trace of globulin. Gastric analysis (histamine) showed free hydrochloric acid present. Roentgenograms of the chest and cervical portion of the spinal column revealed no abnormalities.

Because the urine at the time of one of the urinalyses, in another hospital, was a dark red amber, a specimen of urine was exposed to ultraviolet light. It became pinkish after five minutes' exposure. A test of urine for porphobilinogen gave a positive reaction. Quantitative analyses of the urine, done through the courtesy of Dr. Samuel Nesbitt, University of Minnesota, revealed 254 and 90 gammas of coproporphyrin and 1,574 and 5,270 gammas of uroporphyrin, respectively, in two 24 hour specimens. A third specimen of urine contained 219 gammas of coproporphyrin and 13,400 gammas of uroporphyrin. Spectroscopic analyses, done at the University of Michigan through the courtesy of Dr. Charles Wilkinson, Jr., revealed absorption bands at about 590 to 600 and 540 to 550 millimicrons when the urine was extracted with acetic acid and ether, according to the method of Dobriner and Rhoads. This finding would indicate the presence of uroporphyrin III. This same urine was examined with the Evelyn photo-electric colorimeter with the 420 filter, and gave a quantitative yield of coproporphyrin (ether soluble) of 10 gammas per 100 c.c., or 125 gammas for the entire volume. When examined with Beckman's spectrophotometer, this extract gave a strong absorption band at 400.

The patient was found to be somewhat hypersensitive to ultraviolet light, but not greatly so. Hyperemia was the chief effect. The dosage, however, was kept low.

Evaluation of muscle strength and electrodiagnostic studies.—Voluntary muscle tests taken in November, 1946, January and February, 1947, showed improvement in strength in the trapezius, rhomboidei, latissimus dorsi, pectoralis major, teres major and minor, infraspinatus, supraspinatus, biceps, triceps, deltoids, brachioradialis, extensor carpi ulnaris, palmaris longus, flexor digitorum sublimis and profundus, flexor pollicis longus, flexor carpi ulnaris, interossei dorsales and abductor digiti quinti muscles bilaterally. No improvement in strength or recovery of muscle power was noted during the same interval in the extensor digitorum communis, abductor and extensor pollicis longus, extensor flexor and abductor pollicis brevis, flexor carpi radialis, opponens and adductor pollicis, lumbricales and opponens digiti quinti bilaterally.

Reaction of degeneration was observed mainly in the muscles of the right thenar eminence and the left extensor digitorum longus. Evidence for this type of reaction was seen in the lack of response to faradic stimulation and a slow muscular contraction to galvanic current. No fibrillation of the muscles was observed, but flipping the little finger of the right hand would sometimes set the intrinsic muscles into spasmodic contractions. At times involuntary contractions of the muscles of the shoulder girdles were observed.

Electrodiagnostic data obtained by Capt. E. L. Dillon, M.D.P.T., from the abductor pollicis brevis and extensor digitorum communis of both upper extremities are listed in table 1. The constant current impulse stimulator devised by Golseth and Fizzell and an electromyograph were employed. The galvanic current was used in an interrupted fashion as was the faradic current. In the case of the repetitive stimuli three variances were used, namely 77, 166, and 500 stimulations per second. To determine the galvanic tetanus ratio a stimulus of one and a half seconds' duration with a time interval of four seconds was used.

These studies revealed a loss of response of the muscles to faradic stimulation, lengthening of the chronaxie at the time of first examination with slight decrease on subsequent examinations, loss of normal response to repetitive stimuli, and slight changes in the galvanic tetanus ratios. This evidence indicated diminution and loss of voluntary power in the atrophic muscles. The muscles which were involved followed no definite distribution, but instead presented a patchy pattern. All muscles of

TABLE I  
Electrodiagnostic Data from Abductor Pollicis Brevis and Extensor Digitorum Communis Muscles

	Voluntary Muscle Test*	Response to Stimulation†		Strength Duration Curve	Chronaxie	Repetitive Stimuli	Galvanic Tetanus Ratio	Electromyographic Studies	Atrophy
		Galvanic	Faradic						
Extensor digitorum communis Right Jan. 10, 1947	0	3	0	Continuous	40	Overflow‡ at 14.0 ma.	4.2	Monophasic and polyphasic motor units	Yes
Feb. 25	0	3	0	Continuous	29-40	Overflow at 9.0 ma.	2.6	Monophasic units	Yes
Left Jan. 10	15	3	0	Continuous	20	No tetanus at 11.5 ma.	3.8	Low voltage and low amplitude polyphasic motor units	Yes
Feb. 25	15	2	0	Continuous	20	8.5 ma. Overflow at 12.0 ma.	3.6	Polyphasic and monophasic motor units	Yes
Abductor pollicis brevis Right Jan. 10	0	2	0	Continuous	40	Overflow at 4.5 ma.	4.2	High voltage monophasic motor units	Marked
Feb. 25	0	2	0	Continuous	29-40	Unable to tolerate	2.5	High voltage monophasic motor units	Marked
Left Jan. 10	0	3	0	Continuous	14-20	Overflow at 9.2 ma.	4.3	Low voltage monophasic motor units	Marked
Feb. 25	0	3	0	Continuous	29-29	Overflow at 12.8 ma.	3.1	Low voltage monophasic motor units	Marked

\* 0 = no contraction; 100 = normal contraction.

† 4 = normal response; 0 = no response.

‡ Overflow denotes spread of current to adjacent muscles.



the radial, ulnar and median nerves bilaterally, as well as practically all muscles had, at one time or another, shown a complete loss of or diminution in power. This was most marked in the intrinsic muscles of the hands and the muscles below the elbows supplied by the radial nerve. Atrophy was most marked in the thenar eminences, but was evident in both entire upper extremities. Associated with the atrophy in the muscles of the thenar eminences was the presence of resistance suggesting fibrosis. This fibrosis was discovered when the electromyograph needles were introduced into the muscles of the thenar eminence. Electromyographic studies did not reveal the presence of true fibrillation. Motor units of the monophasic and nascent polyphasic type were observed. The latter type could indicate regeneration although degeneration is not excluded while the former suggests a more normal type of motor unit, especially if the electropotentials are high. Various types of motor units were obtained, ranging from a low voltage polyphasic type to high voltage monophasic type. Squeaking was noted in some muscles, which would indicate that regeneration might be taking place.

No change or only slight change occurred in voluntary power in these muscles from January 10 to February 25, and there was not any change in the response to faradic current or to galvanic current. The strength duration curves showed no discontinuities. There was little change in chronaxie. Repetitive stimuli revealed that the muscles did not react normally, inasmuch as considerable milliamperage was necessary to obtain tetanus, and it could not always be obtained. The galvanic tetanus ratio showed a gradual reduction in the six weeks between tests. This would appear on first glance to indicate a regression in the status of the affected muscles. Actually the findings are within normal limits of neurotization, and probably represent a different group of and more poorly neurotized muscle fibers than those which were tested the first time.

*Treatment and Results.* Hydrotherapy, electrical stimulation to the muscles which would not react voluntarily, and reëducational and strengthening exercises were employed. In addition, occupational therapy, in the form of handicraft that necessitated coördination and movements of the hands and fingers, was prescribed. The patient felt that this treatment not only improved her condition, but kept her from regressing. She was advised to use a liberal diet high in calories and vitamins, and to keep her nutritional state up to a high level, and was encouraged to put on weight. She did improve in general body strength, which was definitely noticeable in the upper extremities and shoulder girdles. The facial weakness and lid lag diminished to such an extent that they could scarcely be recognized. In February, 1947 she had a short, mild episode of muscular aches and pains in her extremities. She was discharged from the service, and the last word on her condition (December, 1947) was that she had improved enough to write legibly, but movement of the thumbs was still poor. Otherwise, she had recovered.

#### COMMENT

It is of interest that porphyria in case 2 had passed as a Guillain-Barré syndrome for approximately 15 months and remained unrecognized in nine different hospitals. In contrast, the condition in case 1 was recognized within the first week that the patient was hospitalized. The feature which led to the diagnosis was the reddish discoloration of the patient's underclothing. However, until the real diagnosis was established, peptic ulcer was thought to be present. The symptoms of abdominal pain characteristic of porphyria have frequently led to surgical exploration, but fortunately these two patients were spared. The case of Halpern and Copsey illustrates how porphyria can simulate coronary occlusion and acute intestinal obstruction, the latter leading to surgery.

Porphyrins apparently cause a spasm of smooth muscle for contraction of the intestinal wall has been observed at operation and spasm of retinal arteries has been seen on fundusoscopic examination. Denny-Brown has said that the pathologic findings could be those associated with ischemia due to intense arteriolar spasm. The effect of arteriolar spasm would be diffuse and extensive; there would be headaches, hyperactive knee jerks, nystagmus, convulsive seizures, hallucinations, somnolence and motor paralysis. Due to the intense arteriolar spasm, the ischemia which results produces degeneration of myelin sheaths and destruction of axis cylinders, if severe. Just why the motor nerves are involved more than the sensory, and why in a patchy way, has not been explained. Nor is it possible to explain why in case 1 there were no neurologic complications, although the urine was red, and in case 2 extensive involvement of the nerves was present although the color of the fresh urine was essentially normal.

Electrodiagnostic data obtained in case 2 are compatible with what other investigators have found at necropsy, namely, that the disease strikes the peripheral nerves, especially the motor component, in a patchy manner. The nerves were sufficiently damaged to produce a reaction of degeneration and abnormal motor unit patterns. Residual atrophy of the muscles was grossly evident over the body, more so in the shoulder girdles and upper extremities, and especially in the small muscles of the hands. Fibrosis was definite in these latter muscles also. Fibrillation was not observed. Its presence would have indicated complete denervation. The fact that it was not observed would suggest that innervation, although poor in the muscles most affected, was not completely cut off. No muscles were found which did not respond at least to galvanic stimulation. Most of the electrodiagnostic data were compatible with that seen in regenerating peripheral nerve injuries.

Clinically the effects on the neuromuscular system did not appear necessarily irreversible in case 2. Some of the muscles probably will never return to normal, but it appeared that many muscles, although they had lost a considerable amount of power, had recovered to an almost normal state. The patient in case 2 was paralyzed in all four extremities at one time, and even had difficulty in breathing and talking. After being bedridden she recovered so that she could again walk, and partially use her arms and fingers. Her thumbs, though, have remained practically useless. The intrinsic muscles of the hands appear to have been affected most permanently, especially those of the thenar eminences. It is logical to assume that, if atrophy occurs in these small muscles, and is present for some time, that a return to a normal condition would be very slow, if at all. The electromyographic findings are in keeping with the postmortem findings reported in other cases of acute porphyria, in that certain motor units were found either in a degenerative or regenerative phase, while others were found in an essentially normal stage, or were intermediate.

#### SUMMARY

Two cases of acute idiopathic porphyria have been reported. One was easily recognized by the characteristic red urine. The other case passed as a case of Guillain-Barré syndrome for more than a year, chiefly because the urine was essentially normal in color when voided. Both cases were characterized during their attacks by acute abdominal symptoms, tachycardia and hypertension. In

one of the cases neurologic complications in the form of muscular paralysis (quadriplegia), bulbar symptoms in the form of dysphonia and dysarthria were noted, but the patient eventually made an almost complete recovery. Muscular atrophy and paralysis persisted in the upper extremities and shoulder girdles. The radial and median nerves were most affected.

Data from electrodiagnostic tests by means of a constant current impulse stimulator and an electromyograph were compatible with postmortem pathologic findings of patchy degeneration of motor nerves. No evidence of complete degeneration was obtained, although there was some evidence of regeneration. Return of voluntary power was noted in some muscles. Muscles which were weakened showed gradual improvement in strength as the disease was allayed and as they were encouraged to further activity.

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## HYPERSPLENISM: TWO CASES WITH LEG ULCERS TREATED BY SPLENECTOMY \*

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SPLENOMEGALY is the common factor in a variety of syndromes of indefinite etiology in which leukopenia, anemia, and thrombocytopenia may be associated disorders. Splenomegaly and leukopenia in rheumatoid arthritis are well known under the name of Felty's syndrome. Chronic leg ulcers have frequently been described in splenomegalic syndromes, and we have recently encountered two cases presenting splenomegaly, atrophic arthritis, anemia, elevated basal metabolism rates, leukopenia with relative and absolute neutropenia, and chronic non-healing leg ulcers.

### CASE REPORTS

*Case 1.* A 59 year old white male entered the hospital on April 2, 1945 complaining of an ulcer on the right shin which had been present for approximately one year. The lesion had first appeared spontaneously as a brownish-red papule which increased in size but did not ulcerate. Five months before admission, the lesion had been excised and promptly healed. However, one month before admission an extremely painful ulcer appeared in the area of excision, making it impossible to bear weight on the extremity. Healing did not follow local application of bland ointments. In addition to this complaint, there had been a crippling arthritis of the hands and "heart attacks" of an indefinite nature, both of approximately 15 years' duration.

*Examination.* The patient was a thin, pale man who appeared chronically ill. Blood pressure was 148 mm. Hg systolic and 90 mm. diastolic; pulse, 120; respirations, 18; temperature, 99.0° F.; weight, 130 pounds. Abdominal examination revealed a prominently enlarged spleen; there was no hepatomegaly. Examination of the extremities revealed ankylosis of the phalangeal joints of the fingers and toes, with atrophy of the overlying skin, prominence of the joints, and ulnar deviation of the fingers (figure 1). On the anterolateral aspect of the lower portion of the right

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leg there was an ulcer measuring 6 by 7 cm. with a black necrotic base surrounded by an area of redness and induration. There was no peripheral edema, and the feet were warm, with reduced but equal peripheral pulses on the two sides. There was no peripheral lymphadenopathy. A few small varicosities were observed in both lower extremities, but the deep venous return was unimpaired.

Admission urinalysis showed a faint trace of albumin, a specific gravity of 1.019, no sugar, and occasional coarse granular casts in the sediment. Hemoglobin was 11.2 gm. (71 per cent); red blood cell count, 3,857,000, and white blood cell count, 3,750, with a differential of 52 per cent segmented neutrophils, 45 per cent lympho-



FIG. 1. *Case 1.* Note extensive crippling arthritis.

cytes, and 3 per cent monocytes. Hypochromia of the red cells was noted in the smear. Non-protein nitrogen content was 19 mg. per cent; total serum protein, 6.1 gm. per cent, with an albumin of 2.9 gm. per cent, and a globulin of 3.2 gm. per cent. The prothrombin amount varied between 87 per cent and 108 per cent of average normal. The platelet count was 350,000; bleeding time, 5 minutes, and clotting time, 3 minutes. Basal metabolism rate was plus 45. Reticulocyte count was 5 per cent. The blood Kahn reaction was negative.

Repeat white blood cell counts varied between 2,250 (April 7), 825 (April 10), 1,800 (May 8), and 2,250 (July 7, 1945), the differential for the white blood cell

count of 825 showing 2 per cent immature myelocytes, 2 per cent juveniles, 3 per cent stabs, 28 per cent segmented neutrophils, 43 per cent lymphocytes, 5 per cent abnormal monocytes, 9 per cent immature monocytes, 5 per cent monocytes, and 3 per cent eosinophiles.

A roentgenogram of the chest showed a slight increase in the linear and hilar markings and an old scarring at the right apex. A film of the right leg showed calcification of the tibial vessels, cortical thickening, and increased cortical density underlying the ulcerated area. Arthritic changes were noted in the joints of the knees, wrists, hands and digits, with areas of diminished bone density and narrowing of the joint spaces.

*Course.* Three biopsies of the leg lesion revealed acute and chronic inflammation. A sternal bone marrow biopsy showed innumerable nucleated red cells, many cells of the myeloid series in various stages of transition, and focal areas of mature and immature myelocytes. There was no evidence of leukemia. The hemoglobin and red blood cell count responded poorly to transfusion, and because of auto-agglutination, difficulty was encountered in the administration of blood. The lesion did not respond to débridement, and following numerous transfusions (on the presumptive diagnosis of aleukemic leukemia) roentgen therapy was given over a period of eight days without improvement. Subsequent to this therapy, the ulcer was débrided on two other occasions, followed by frequent dressings and mechanical cleansing, and roentgen therapy to the leg lesion was given over a period of 11 days, again without appreciable improvement. The lesion began to evidence slight infection, and 10,000 units of penicillin were given parenterally every three hours. A cephalin cholesterol flocculation test was 4 plus, and there was 15 per cent retention of bromsulfalein after 30 minutes.

In spite of these measures, the ulcer progressively enlarged and the patient gradually lost eight pounds weight. The white blood cell count remained persistently low, and lymphocytes predominated at the expense of a reduction in the granulocytic series.

On the sixty-fifth hospital day (June 20, 1945) a 1,540 gm. purplish-gray spleen was removed. The splenic vessels appeared normal, and samples of blood taken from them gave the following determinations:

<i>Blood from Vein</i>	
Hemoglobin	12.9 gm. 82%
Red cell count	4,560,000
White cell count	670
Differential:	
Myeloblasts	0%
Myelocytes	5%
Juveniles	7%
Stabs	16%
Segmented	
neutrophils	16%
Lymphocytes	54%
Monocytes	2%
Basophiles	0%
Platelets	180,000

<i>Blood from Artery</i>	
Hemoglobin	13.8 gm., 88%
Red cell count	5,000,000
White cell count	825
Differential:	
Myeloblasts	1%
Myelocytes	5%
Juveniles	0%
Stabs	17%
Segmented	
neutrophils	30%
Lymphocytes	36%
Monocytes	5%
Basophiles	2%
Platelets	280,000

Microscopic examination of the spleen showed slight congestion but no evidence of leukemia, amyloid disease, Hodgkin's disease, or any specific inflammatory processes. There was an increase of plasma cells and of nucleated red cells, but no increase in connective tissue and no phagocytosis of white cells. The changes observed were interpreted as being consistent with chronic infection of long duration.

Postoperatively, the patient's temperature rose to 100.6° F. on one occasion, but otherwise it did not go above 100.0° F. A minimal atelectasis of the right upper chest was transitory, and an epididymitis responded to roentgen therapy. A white count on the second postoperative day was 17,800; on the fifth day it was 5,800 with a differential of 3 per cent juveniles, 27 per cent stabs, 63 segmented neutrophils, 6 per cent lymphocytes, and 1 per cent monocytes. The sixth and seventh days leukocyte counts were similar. Subsequently the white blood cell count varied between 1,400 and 3,700 with an average of 30 per cent to 40 per cent stabs, 20 per cent to 30 per cent segmented neutrophils, and 20 per cent to 35 per cent lymphocytes. Prothrombin content remained above 75 per cent of average normal, and gradually increased to 93 per cent.

Following splenectomy, the ulcer improved rapidly under wet dressings and mechanical cleansings, and pinch grafting was successfully accomplished. (Prior to splenectomy, attempts at grafting could not be considered.) At discharge on the thirty-fourth postoperative day, the hemoglobin was 13.1 gm. (83 per cent); red blood cells numbered 4,362,000, white blood cells, 2,900, with a differential of 24 per cent stabs, 19 per cent segmented neutrophils, 47 per cent lymphocytes, 2 per cent basophiles, and 8 per cent eosinophiles. Basal metabolism rate was plus 22.

Four months after discharge from the hospital (October 24, 1945) the patient was readmitted for extensive study, evidencing a weight gain of 35 pounds and striking improvement in his color and general appearance. The leg ulcer was completely epithelialized. There was no pain, and no confinement to bed. Urinalysis still showed a trace of albumin; the non-protein nitrogen content was 22 mg. per cent; total protein, 7.0 gm. per cent, with an albumin of 4.5 gm. per cent, and a globulin of 2.5. The hemoglobin was 15.4 gm. (98 per cent); red blood cells numbered 4,850,000; white blood cells 3,100; juveniles, 16 per cent; stabs, 8 per cent; segmented neutrophils, 2 per cent; lymphocytes, 60 per cent; and eosinophiles, 14 per cent. The prothrombin amount was 81 per cent of average normal; basal metabolism rate, plus 15; and platelet count, 120,000. A cephalin cholesterol flocculation was three plus, and there was no retention of bromsulfalein after 30 minutes. Reticulocyte count was 1.2 per cent. Sternal marrow biopsy showed questionable slight hyperplasia with a questionable increase in the erythroblastic elements and some increase in plasma cells. These findings were essentially the same as before splenectomy. Following these studies, the patient was discharged.

Two months later, December 23, 1945, he was again admitted to the hospital, this time with two zones of ulceration within the area of pinch grafting. These nonpainful lesions had become manifest shortly after sequestration of a small bone fragment, and resembled in appearance those seen on the first admission.

Laboratory studies at this admission revealed a blood count of: hemoglobin, 13.4 gms. (85 per cent); red cell count, 5,280,000; white cell cells, 2,850; juveniles, 1 per cent; stabs, 2 per cent; segmented neutrophils, 8 per cent; lymphocytes, 61 per cent; monocytes, 26 per cent; and eosinophiles, 2 per cent. Platelet count was 200,000. Bleeding time was 35 seconds; clotting time, 3½ minutes. The reticulocyte count was 0.1 per cent. Urine showed a trace of albumin, no sugar, a specific gravity of 1.016, and numerous red cells and occasional hyaline casts in the sediment. Basal metabolism rate was plus 24; icteric index, 5; non-protein nitrogen content, 18 mg. per cent; total protein, 8.4 gm. per cent, with an albumin of 3.7 gm. per cent, and a globulin of 4.7. Cephalin cholesterol was 4 plus, and there was no bromsulfalein retention after 30 minutes.

Roentgenograms of the leg again showed cortical thickening and a small amount of periosteal proliferation. The sternal bone marrow showed no change from the preceding biopsies. A biopsy of the calf muscle on the affected side was normal. A high saphenous vein ligation and retrograde injection were performed at this admis-

sion, although no great benefit was anticipated. Fifteen days following admission, he was discharged.

At the fourth admission two months later the ulcers of the leg had coalesced, and the total area now measured 7 by 8 cm., an increase in size since the previous admission (figure 2). Laboratory determinations were similar to those of the previous admissions except that the urine was free of albumin and the sediment was negative. A roentgenogram showed a slight increase in the periosteal reaction previously noted. The patient's general condition was poor, and in truth he was in much the same state as when first seen. He was discharged after five days of hospitalization.



FIG. 2. Case 1. Area of extensive ulceration with infection eight months following splenectomy. Note complete failure of healing.

One and one-half months later, on April 6, 1946 (one year following the first examination, and 291 days following splenectomy) the patient died at his home. The family physician reported that the patient developed increasing infection and extension of the ulcer of the leg, with hemorrhage from that area. Frequent epistaxis and coughing up of blood suggested a bleeding tendency. In addition, the patient ran a high temperature and developed a throat infection. Permission for postmortem examination was not obtained.

*Case 2.* For eight months previous to entry on April 13, 1945, this 50 year old white female had an ulcer on the left leg, which (without antecedent trauma) had



first appeared as a small red spot. Coal oil and bland salve were applied, but small blisters appeared about the reddened area and the patient then consulted her family physician, who treated the lesion by cleansing and débridement of the blisters. In spite of this, an ulceration formed which gradually increased in size. There was also a history of deforming arthritis of 10 years' duration resulting in ankylosis of the finger and knee joints, progressive weakness concomitant with 12 pounds weight loss, and increasing nervousness and insomnia during the two months prior to admission. Family history and past history were noncontributory.

*Examination.* The patient was a thin, undernourished woman with evidence of weight loss. Blood pressure was 90 mm. Hg systolic and 52 mm. diastolic; pulse, 80; respiration, 18; temperature, 101.2° F., and weight, 87 pounds. The thyroid was thought to be slightly enlarged, but no bruit was heard. The left diaphragm was elevated. The heart was of normal size and shape, the rhythm regular, and a rough, blowing systolic murmur was heard at the apex and transmitted to the axilla.



FIG. 3. Case 2. Advanced atrophic arthritis. Note similarity to Case 1.

Abdominal examination revealed an enlarged spleen in the left upper quadrant, extending well below the level of the umbilicus. The liver was also slightly enlarged to palpation. There was no peripheral lymphadenopathy. A fixed flexion deformity of the knees was present, and the fingers showed ulnar deviation, flexion, and ankylosis, with prominence of the phalangeal and metacarpophalangeal joints (figure 3). On the lower third of the left leg a huge, necrotic, malodorous ulceration was observed, which was almost completely annular and measured 16 cm. in diameter. The edges of this lesion were slightly raised, the base black and secondarily infected, and there was little induration but considerable redness surrounding the ulceration (figure 4). There were no varicosities of either extremity; the right dorsalis pedis pulse was present, but a pitting edema of the left foot obscured the pedal pulse. Pelvic and rectal examinations were not unusual.

Admission blood work revealed a hemoglobin of 5.9 gm. (37 per cent), red cell count, 2,310,000; white cell count, 3,600; 4 per cent juveniles; 22 per cent stabs; 42 per cent segmented neutrophils; 25 per cent lymphocytes; 5 per cent myelocytes;

1 per cent monocytes, and 1 per cent eosinophiles. On smear, the red cells showed marked hypochromia. Non-protein nitrogen was 14 mg. per cent, and total serum protein was 7.7 gm. per cent, with an albumin of 3.0 and a globulin of 4.7. A trace of albumin was found in the urine. The blood Kahn reaction was negative. A fasting blood sugar was 88 mg. per cent; basal metabolism rate was plus 80; urine examined for Bence-Jones protein was negative, and a blood culture was also negative. A culture from the ulcer showed unidentified spirochetes and gram positive cocci occurring in clusters and short chains.

A radiograph of the chest showed elevation of the left diaphragm, small calcified areas in the hilar regions, and somewhat thickened linear markings. Roentgenogram of the left leg showed demineralization and slight periosteal proliferation along the posteromedial aspect of the distal third of the tibia, and films of the knees and hands showed thinning of the joint spaces, with complete obliteration of some of the joints of the hands. Flexion deformities were noted in the digits, and demineralization of bone was present throughout. The changes were typical of rheumatoid arthritis.

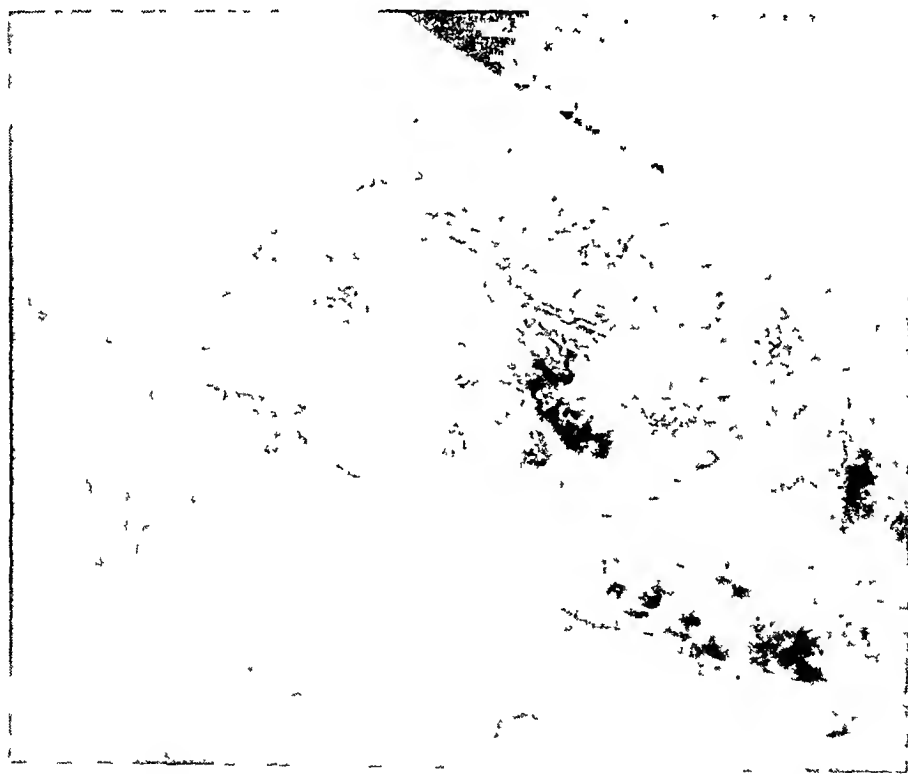


FIG. 4. Case 2. Area of extensive ulceration of leg which failed to heal before splenectomy.

*Course.* Zinc peroxide dressings were placed on the leg ulcer, and the patient was given multiple transfusions. Following the third transfusion, the hemoglobin rose to 7.9 gm. (50 per cent), red blood count was 2,250,000, and white blood count 3,500. The differential at this time was: 6 per cent myelocytes, 7 juveniles, 38 stabs, 15 segmented neutrophils, 32 lymphocytes, and 2 monocytes. A sternal marrow biopsy showed slight hyperplasia and an increase in plasma cells. Proliferation of cells of the reticulo-endothelial system was suggested.

Exploratory laparotomy, with biopsy of the enlarged liver and spleen, was next performed. On microscopic examination, the liver showed an increase of glycogen

deposition but was otherwise not unusual. The spleen showed slight fibrous thickening of the capsule, some dilatation of the sinusoids, evidence of extramedullary hematopoiesis, increase in plasma cells, and increase in cells of the myeloid series. The endothelial lining cells of the sinusoids were not overly prominent, and there was no increase in connective tissue.

Additional transfusions were given, and the patient was prepared for splenectomy which was performed on May 15, 1945, the thirty-third hospital day. At operation, a 1,300 gm. spleen was successfully removed. There was no evidence of thrombosis or constriction of splenic vein, and specimens of blood obtained from the artery and splenic vein gave the following determinations:

<i>Blood from Artery</i>		<i>Blood from Vein</i>	
Hemoglobin	10.7 gm., 68%	Hemoglobin	11.6 gm., 74%
Red cell count	3,591,000	Red cell count	3,857,000
White cell count	2,050	White cell count	1,900
Differential:		Differential:	
Myelocytes	6%	Myelocytes	4%
Juveniles	0%	Juveniles	2%
Stabs	14%	Stabs	18%
Segmented		Segmented	
neutrophils	20%	neutrophils	6%
Lymphocytes	60%	Lymphocytes	68%
Monocytes	0%	Monocytes	2%
Platelets	300,000	Platelets	420,000

The spleen contained a small hemangioma and a lymphangioma. Microscopic examination showed no phagocytosis of the white cells, but did show changes similar to those observed in the biopsy tissue. The findings were thought to be consistent with those of rheumatoid arthritis and infection, and contrary to the dubious attitude held by the Staff concerning the ultimate benefit of such a surgical procedure, the response was remarkable. On the first postoperative day the patient had a temperature elevation to 101.0° F., which dropped to 100.4° F. the second day, and thereafter was normal. White blood count on the first postoperative day was 2,450, with 2 per cent eosinophiles, 1 per cent juveniles, 34 per cent stabs, and 29 per cent lymphocytes. Platelet count was 390,000; prothrombin content was normal. On the second day the white count was 10,500, with 1 per cent myelocytes, 3 per cent juveniles, 20 per cent stabs, 73 per cent segmented neutrophils, and 3 per cent lymphocytes. The white count gradually decreased, while the prothrombin content of the blood increased. Twenty-eight days postoperative the white count was 5,100, with 1 per cent juveniles, 1 stab, 57 segmented neutrophils, 37 lymphocytes, 2 monocytes, and 2 eosinophiles. The basal metabolism rate was still abnormal, remaining plus 80. The leg ulcer showed marked improvement, clean granulations now appeared, and a split graft applied to the leg ulcer was approximately 70 per cent successful. The right lobe of the thyroid was resected on June 26, 1945, and microscopic examination of the tissue revealed a benign fetal adenoma. Three days postoperative the basal metabolism rate was plus 72. The patient was discharged on the eighty-first hospital day.

A clinic visit four months later showed a weight gain of 14 pounds and complete healing of the leg ulcer and all operative wounds. The patient displayed a healthy, flushed appearance of the skin and mucous membranes. A count at that time revealed a hemoglobin of 15.5 gm. (99 per cent), red blood cells 4,868,000; white blood cells 3,350; 7 per cent stabs; 32 per cent segmented neutrophils; 59 per cent lymphocytes, and 2 per cent monocytes.

Five months later the patient was readmitted to the hospital for study. The leg ulcer was still well healed and showed no tendency toward degeneration. There had been a further weight gain of five pounds. Urinalysis showed a trace of albumin and a specific gravity of 1.020; there were a few red cells and occasional granular casts in the sediment. Hemoglobin was 15.4 gm. (98 per cent); red cell count, 5,060,000; white cell count, 3,400; stabs, 16; segmented neutrophils, 32; lymphocytes, 40; monocytes, 4; and eosinophiles, 8 per cent. Hematocrit was 48 per cent; prothrombin content, 93 per cent of normal; platelet count, 230,000; icteric index, 4; non-protein nitrogen, 20 mg. per cent; cephalin cholesterol flocculation, 4 plus; bleeding time, 2 minutes; clotting time,  $2\frac{1}{4}$  minutes; and fragility test was normal. Basal metabolism had dropped to plus 28.



FIG. 5. Case 2. Complete healing of the area of ulceration 22 months after splenectomy.

This patient was last seen on March 12, 1947, 22 months after splenectomy. She was in excellent general condition. Her arthritis remained stationary, the leg was well healed (figure 5), and bleeding time, clotting time, and icteric index were normal. The platelet count was 200,000, and the complete blood count was as follows: Hemoglobin 16.8 gm., 116 per cent; red blood cells 5,640,000; white blood cells 12,900; stabs 8, segmented neutrophils 29, lymphocytes 53, monocytes 8, eosinophiles 1, and basophiles 1 per cent.

#### DISCUSSION

In each case following splenectomy there were several significant changes for the better. Over a short period of time there was a gain of weight (14 pounds and 45 pounds), appreciable improvement in the general condition, and an increase in physical activity. In each case the red cell count and hemoglobin

returned to normal. In the white blood cell picture, a temporary alteration to a normal level gradually gave way to the previous leukopenic-neutropenic state. There was a diminution in the basal metabolism rate. Most encouraging was the initial improvement in the leg ulcers. Previous to splenectomy, meticulous local cleanliness and débridement had caused no improvement in the ulcers; following operation, healthy granulations appeared, and complete epithelialization was accomplished by skin grafting. Unfortunately, in the first case the ulcer recurred with the shedding of a small bone sequestrum; in all respects the lesion assumed its former appearance; the patient failed rapidly, and finally died. Leukopenia and granulocytopenia were present and clinical signs before death suggested a bleeding tendency. In the second case the ulcer has remained epithelialized and the patient is in excellent health. Leukopenia and granulocytopenia similar to the admission state are present, but the red blood cell series have persisted within normal limits since splenectomy.

These two cases do not present the common etiologic conditions causing chronic leg ulceration. There was no evidence that the ulcers were primarily infectious and vascular changes were at a minimum. In particular, syphilis and tuberculosis were excluded, and neoplastic disease was eliminated immediately by biopsy.

These two cases presented unmistakable joint alterations typical of rheumatoid arthritis. The arthritis was far advanced and quiescent, and there was no complaint referable to the joints other than loss of function due to ankylosis. There was no change in the condition of the joints following splenectomy. The basal metabolic rate in rheumatoid arthritis is usually normal and is more often subnormal than elevated,<sup>1, 2</sup> but both of our cases had basal metabolic rates elevated to values rarely encountered in rheumatoid arthritis. Although to our knowledge chronic leg ulcers of uncertain etiology have not been encountered in rheumatoid arthritis, Steinbrocker and Samuels,<sup>3</sup> in a careful study of the peripheral vascular status in rheumatoid arthritis, found vasomotor abnormalities in 65.9 per cent. These abnormalities were usually reflected in a reduction of arterial circulation. The authors did not record significant skin changes other than those usually associated with rheumatoid arthritis, and no case of leg ulceration was mentioned. Vascular alterations in our two cases were certainly no greater than those observed by Steinbrocker and Samuels, yet ulceration was present in each. Certainly an etiology other than vascular was suggested in these two cases.

Splenomegaly is found in 10 to 20 per cent of all cases of rheumatoid arthritis.<sup>1, 4</sup> Mild leukopenia with a relative lymphocytosis is not uncommon,<sup>5</sup> and liver dysfunction is found in 50 to 60 per cent of cases of severe rheumatoid arthritis.<sup>2</sup> Lymphadenopathy is present in 40 to 60 per cent and hypochromic anemia and weight loss are common.<sup>5, 6</sup> In 1924, Felty<sup>7</sup> reported several of these abnormalities occurring simultaneously in five cases, all of middle age (45 to 65 years) and showing marked weight loss (40 to 64 pounds) in four patients. There was rheumatoid arthritis of four and one-half years' average duration, splenomegaly, lymph node enlargement (axillary, inguinal, and epitrochlear) in three cases, slight secondary anemia in four, and marked leukopenia (1,000 to 4,200). Additional characteristics consisted of marked joint symptoms with rather benign objective changes, a yellowish-brown skin pigmentation, and a low-grade fever (two patients).

Our cases had characteristics similar to Felty's syndrome. However, lymphadenopathy and skin pigmentation were not observed, and in Felty's original report and in subsequent reports, leg ulcers were not observed.

The bone marrow biopsy in Felty's syndrome has consistently shown a hyperplasia,<sup>8, 9, 10, 11, 12</sup> as was found in our cases. Steinberg<sup>9</sup> observed identical changes in the bone marrow of 12 cases of rheumatoid arthritis without the picture of Felty's syndrome. Examination of the spleen in Felty's syndrome, where possible, has shown dilated sinuses,<sup>8, 10, 12, 13, 14, 15</sup> increased numbers of plasma cells,<sup>8, 10, 12, 14, 15</sup> erythrophagia,<sup>8, 12, 13, 14, 15</sup> increased numbers of eosinophiles,<sup>10, 15</sup> hyperplasia of the lining cells of the sinusoids,<sup>8, 14</sup> increased red pulp,<sup>8</sup> and diffuse fibrosis and myeloid activity.<sup>10</sup> Our cases showed dilated sinusoids and an increase in plasma cells. The picture was thought to be consistent with a chronic infectious process, and this interpretation has been placed on the changes in the spleen in Felty's syndrome.<sup>10</sup>

Splenectomy has been performed in Felty's syndrome with varying results. Hanrahan and Miller<sup>14</sup> reported the first splenectomy in 1932 with a marked improvement in the arthritis, anemia, leukopenia, and thrombocytopenia up to four months. Craven,<sup>15</sup> in 1934, reported a transient beneficial effect on the arthritis and the leukopenia for eight months, a disappearance of abnormal skin pigmentation, and an improvement in liver function following splenectomy. In 1935 Fitz<sup>16</sup> reported that Hanrahan and Miller's case died 18 months after operation and Craven's case died of general inanition and terminal lobular pneumonia 14 months postoperatively. In 1942 Steinberg<sup>9</sup> reported an improvement in general health and leukopenia following splenectomy but with an evident tendency to reversion to the former state. More encouraging are the cases of Zimmer<sup>11</sup> and Hirschboeck.<sup>12</sup> Splenectomy performed in one of Zimmer's cases resulted in loss of joint pains and a reversion of the blood picture to normal for 19 months. Hirschboeck reports one case of improved joint function and a normal blood picture for five years following splenectomy. His second case demonstrated a leukocytosis and granulocytosis for six weeks, at which time the patient succumbed to a pyelophlebitis. The immediate results in our cases were also good, and persistent benefit is expected in the second case. However, leukopenia recurred in both.

It is evident that many of the distinguishing features of these two cases are not unknown in rheumatoid arthritis and Felty's syndrome. All of Felty's original cases showed skin pigmentation, although subsequent investigators have not always included this feature in their diagnostic criteria. The basal metabolic rates in our cases are suggestive of some other process, and leg ulcers have not been reported in Felty's syndrome.

The introduction of the entity primary splenic neutropenia by Wiseman and Doan<sup>17</sup> in 1939 and the relating of this disease to congenital hemolytic jaundice and essential thrombocytopenic purpura were important steps forward in the understanding of splenic physiology and function. Wiseman and Doan<sup>18, 19</sup> have now reported six cases of this disease and five additional cases have been reported by other authors.<sup>20, 21, 22, 23, 24</sup> The syndrome is characterized by marked neutropenia and splenomegaly. Histologic identification rests on the demonstration of phagocytosis of granular leukocytes of the circulating blood by the reticuloendothelial cells of the spleen, according to Wiseman and Doan.<sup>18</sup> This phagocytosis is a reflection of an accelerated destruction of granulocytes in the

spleen. The cases reported by Muether et al.<sup>22</sup> and Rogers and Hall<sup>23</sup> did not show phagocytosis of the granulocytes but were in all other respects similar, and Wiseman and Doan have accepted the case of Muether. Supravital staining more clearly demonstrates the phagocytosis, and this technic was not employed in the cases of Muether and Rogers and Hall. Splenectomy is apparently permanently curative; this is substantiated in all reports. Bone marrow studies show hyperplasia of the myeloid elements (also of the red cell series if hemolytic anemia is pronounced).

As previously mentioned, the relationship of splenic neutropenia to hemolytic anemia and thrombocytopenia is emphasized by Wiseman and Doan. It is pointed out that in the latter two diseases excessive destruction of red cells and platelets occurs in the spleen, and identical changes in varying degrees may be seen in primary splenic neutropenia. Associated icterus and purpura may be symptoms and signs in splenic neutropenia. There is a favorable response of all elements to splenectomy. Doan and Wright<sup>19</sup> have recently reported a case of congenital splenic panhematopenia in which there was a hemolytic anemia, thrombocytopenia, and granulocytopenia attributed to excessive destruction of the respective blood elements in the spleen.

Witts<sup>25</sup> has reported two cases of chronic leg ulcers in association with essential thrombocytopenic purpura. In neither case was the spleen palpable. Both the ulcers and the thrombocytopenia responded to splenectomy in the first case, but removal of the spleen caused no improvement of the ulcers or the platelet count in the second case. In 1940, Leger and Orr<sup>26</sup> reported two cases of leg ulcer associated with congenital hemolytic jaundice. Both conditions responded to splenectomy in each case. Wiseman and Doan's third case of primary splenic neutropenia, reported in 1942, had a chronic ulceration of the leg which had failed to respond to any treatment but which healed promptly following splenectomy. In addition, this patient had a basal metabolism rate of plus 26, and intermittent swelling and tenderness of various joints. Joint symptoms were also a feature of the first case. In the case of congenital splenic panhematopenia reported by Doan and Wright, there were recurrent skin lesions. Following splenectomy there was a reversion of the blood picture to normal and no further skin disorder appeared.

Certainly neither of our cases could be classified as a hemolytic anemia or a thrombocytopenic purpura. The absence of phagocytosis of the granular leukocytes in the spleen, and the ultimate indifferent response of the peripheral blood leukocytes to splenectomy would militate against the diagnosis of primary splenic neutropenia. Each case does show, however, a marked improvement in the pre-existing anemia after splenectomy, as well as a temporary leukocytosis.

Other conditions which merit brief consideration are Banti's syndrome, sickle-cell anemia, leukemia, agranulocytosis, and Gaucher's disease. In the two cases we have reported, there was splenomegaly, anemia, and leukopenia, but no evidence of gastrointestinal hemorrhage. At operation the splenic vessels demonstrated no abnormality and examination of the spleen showed no significant increase in connective tissue. Leg ulcers are common in sickle-cell anemia, but the other identifying features such as sickling of the red cells, jaundice, leukocytosis rather than leukopenia, are absent in our cases. The diagnostic alteration in the bone marrow and spleen and the other obvious clinical features of leukemia,

agranulocytosis, and Gaucher's disease are not present in our two cases. However, it is of some interest that Lockie et al.<sup>8</sup> made a provisional diagnosis of leukemia, later corrected, in their case of Felty's syndrome and also instituted roentgen therapy, as in our first case. Leg ulcers have been reported in myelogenous leukemia,<sup>27</sup> but this is extremely rare.

We have been unable to fit our cases into any previously described clinical pattern, although they are in some respects similar to many. We have been unable to identify pathologic features which are unique. On the other hand, the clinical response to splenectomy appeared clear. There was a marked improvement in the total blood picture, although leukopenia recurred in each instance. A normal erythrocyte picture has persisted. There was a marked improvement in the leg ulcers with eventual complete epithelialization, but this was only temporary in one case. Whether this change in the leg ulcers is a reflection of the improved blood picture or whether it is due to the removal of some noxious agent with the spleen cannot be stated. There was an improvement in the general physical condition, which has persisted. The basal metabolism rate has shown a decrease commensurate with the correction in anemia, but it still remains well above normal levels.

The question naturally arises whether this is a distinct clinical entity or a combination of two or more, arising in the same individual, and there is no certain answer. When Wiseman reviewed these two cases it was suggested by him that probably more than one factor was at work in both of these patients. He felt that part of the granulocytopenia was due to hypersplenism with excessive destruction of the blood elements. It was suggested that the longer the granulocytopenia and chronically infected leg ulceration existed, the more difficult a permanent cure becomes. Added to this is a possible permanent inhibitory effect on the bone marrow by an unknown agent secondary to hypersplenism. He then suggested that following splenectomy, an improvement in the blood picture and leg ulcers could be predicted (as had occurred when he reviewed the cases), but subsequently a fall in the leukocyte count—and even recurrence of the ulceration—might be expected because of the other factors tending to produce granulocytopenia in these cases; namely, rheumatoid arthritis and chronic infection of long standing. That destruction of granulocytes in the spleen may, not be of great importance in our cases is suggested by the essentially identical white blood cell counts taken from the splenic artery and splenic vein at the time of splenectomy in each case. This finding is in accord with the failure to demonstrate phagocytosis in the spleen. Hirschboeck<sup>12</sup> was able to show a white cell count of 11,700 in splenic arterial blood as against a count of 2,600 in splenic venous blood in a case of Felty's syndrome subjected to splenectomy. However, he did not observe phagocytosis of granulocytes in the spleen and favored a combination of the theories of splenic inhibition of the bone marrow and splenic phagocytosis in explanation of the leukopenia of hypersplenism. Recently Doan and Wright<sup>19</sup> have reported a case of splenic panhematopenia secondary to Gaucher's disease. Other similar cases were cited and it was hypothesized that splenic panhematopenia may occur secondary to many other diseases in which there is an associated hypersplenism. Perhaps the splenomegaly of rheumatoid arthritis through excessive destruction of blood elements and/or bone marrow inhibition might lead to a pancytopenia.



## SUMMARY

Two cases are reported which are characterized by rheumatoid arthritis, splenomegaly, chronic leg ulcer, leukopenia and neutropenia, anemia, and elevated basal metabolism rate. Splenectomy has been of persistent benefit in one case (22 months following splenectomy). These cases do not appear to allow classification among well-recognized syndromes.

*Addendum.* The patient was again seen April 7, 1948, 35 months after splenectomy. She had no complaints, was gaining weight and the grafted area remained healed. Blood count showed RBC 5,350,000, hemoglobin 15 gm. (100 per cent), WBC 7,750 with stabs 8 per cent, segmented neutrophils 53 per cent, lymphocytes 34 per cent, monocytes 4 per cent, eosinophils 1 per cent. Platelet count 220,000.

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## A CASE OF CYSTIC FIBROSIS OF THE PANCREAS ASSOCIATED WITH CHRONIC PULMONARY DISEASE AND CIRRHOSIS OF THE LIVER \*

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### INTRODUCTION

CYSTIC fibrosis of the pancreas is a rare disease of infancy and childhood which usually has a fatal termination within the first two years of life. This case is unusual in that the age at death was 17 years.

### CASE REPORT

A 17 year old boy was admitted to the medical service of the Toronto General Hospital, February 19, 1946, because of increasing shortness of breath, and died on March 30, 1946. His father stated that he had never been a robust child, and that since shortly after birth he had had about five daily bowel movements which were bulky, pale, soft, and very foul smelling. At the age of 10 years he contracted measles, followed by pneumonia. This illness was of 13 weeks' duration and was treated at another hospital. Ever since the above illness there had been a slight unproductive cough and undue shortness of breath when playing games; clubbing of the fingers and toes was first noted then. After September 1945 the shortness of breath on effort increased and was accompanied by slight swelling of the legs.

On January 2, 1946, he was examined by a private physician who noted that he was undernourished, and found persistent medium râles over both lower lung fields, moderate enlargement of the liver and edema of the ankles. About two weeks prior to admission a nasal discharge and malaise developed followed by increase in cough, which became productive of mucopurulent sputum. He continued to attend school, however, until 10 days before admission, when he was forced to remain in bed be-

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cause of increasing dyspnea, even at rest, and the development of a sharp stabbing pain over both sides of the lower chest posteriorly.

On examination he appeared acutely ill, was moderately dyspneic propped up in bed, and slightly cyanosed. He appeared underdeveloped. He was coughing oc-



FIG. 1. Section of right lung showing scattered areas of consolidation, bronchiectasis, and enlarged peribronchial lymph nodes.

asionally and expectorating thick mucopurulent sputum. The rectal temperature was 103° F., the pulse rate was 110 per minute, and the respiratory rate 32. The jugular veins were not engorged. Blood pressure 110 mm. of mercury systolic and 50 mm. diastolic. The heart and trachea were in normal position. The chest was

barrel-shaped. Respiratory movement of the chest was reduced on both sides, more so over the left base. The lower borders of the lungs were one interspace lower than normal and there was loss of superficial cardiac dullness. The breath sounds were

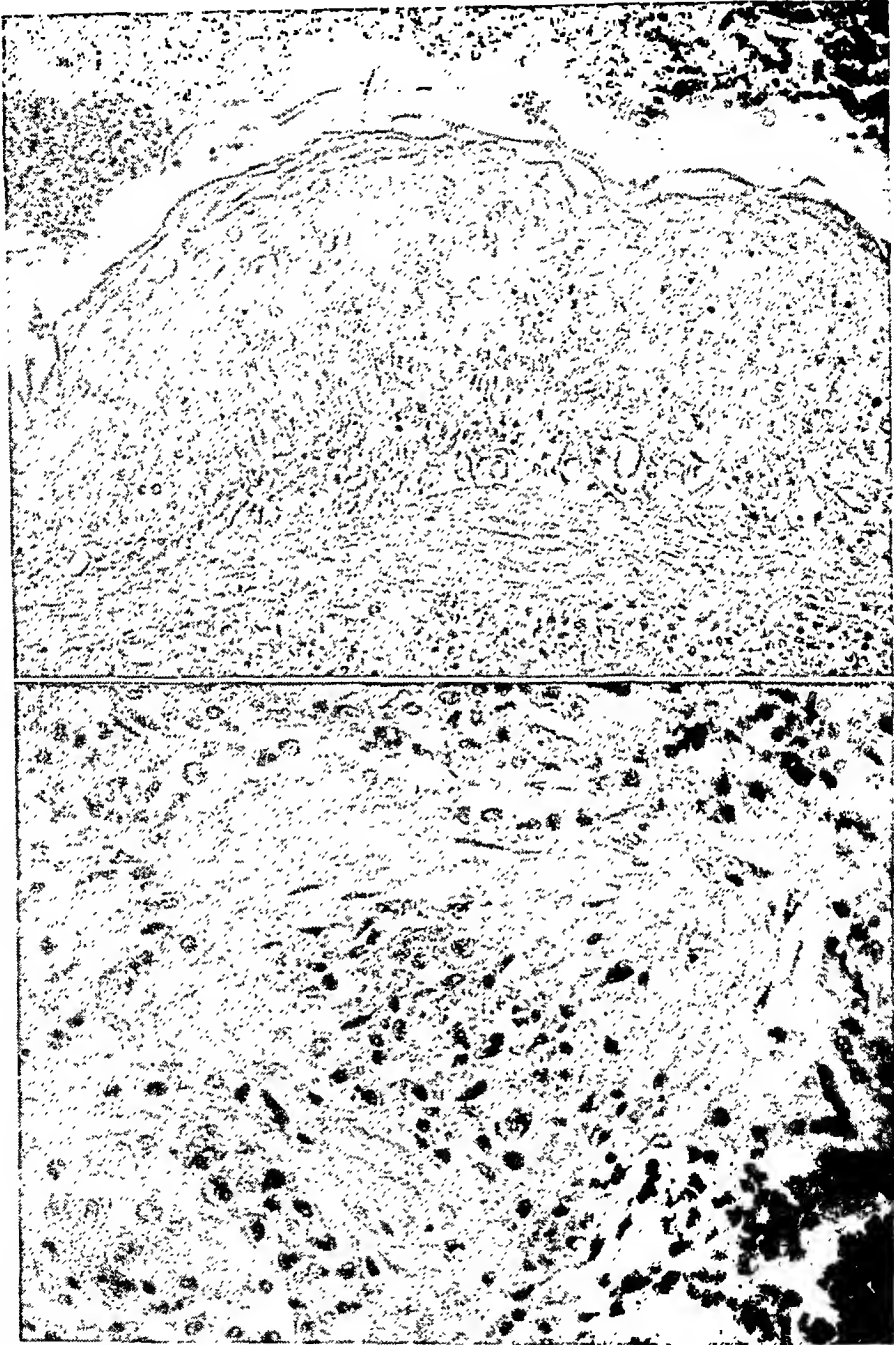


FIG. 2 (*Above*). Squamous metaplasia of bronchial epithelium.  $\times 155$ .  
FIG. 3 (*Below*). Organization of pneumonia exudate.  $\times 335$ .

intense and vesicular in type. Numerous fine and medium râles were heard throughout both lung fields, especially at the bases. A friction rub was present over the lower chest posteriorly on both sides. The abdomen was distended and tympanitic. The liver was moderately enlarged; the surface felt smooth and firm. The spleen

was not palpable. There was no edema of the extremities. The fingers and toes were moderately clubbed. Neurological examination was negative except for absence of knee reflexes.

Urinalysis was negative. Hemoglobin 87 per cent; red cell count 4,700,000; white cell count 20,600, with a differential count of 94 per cent neutrophils. The red cells were normal in size, shape, and hemoglobin content. The stools were bulky, pale, soft and very foul smelling and the total fat content was estimated to be 66 per cent of the dry weight. Serum calcium 8.2 mg. per cent; serum phosphorus 4.3 mg. per cent; alkaline serum phosphatase 47 units. Van den Bergh, negative direct, 0.4 unit. Serum proteins: total 7.8 gm. per cent composed of albumin 4.0 and globulin 3.6 gm.; fractionation at 13.5 per cent sodium sulfite 1.5 per cent; formol-gel 4+. Prothrombin time normal. Galactose tolerance test normal. Electrocardiogram showed sinus tachycardia. The sputum on culture grew many colonies of *Staphylococcus aureus hemolyticus*. Blood cultures were sterile. Chest roentgen-ray showed evidence of scattered areas of peribronchial infiltration throughout both lung fields. Roentgen-rays of the long bones revealed a moderate degree of diffuse osteoporosis, but no other abnormality.

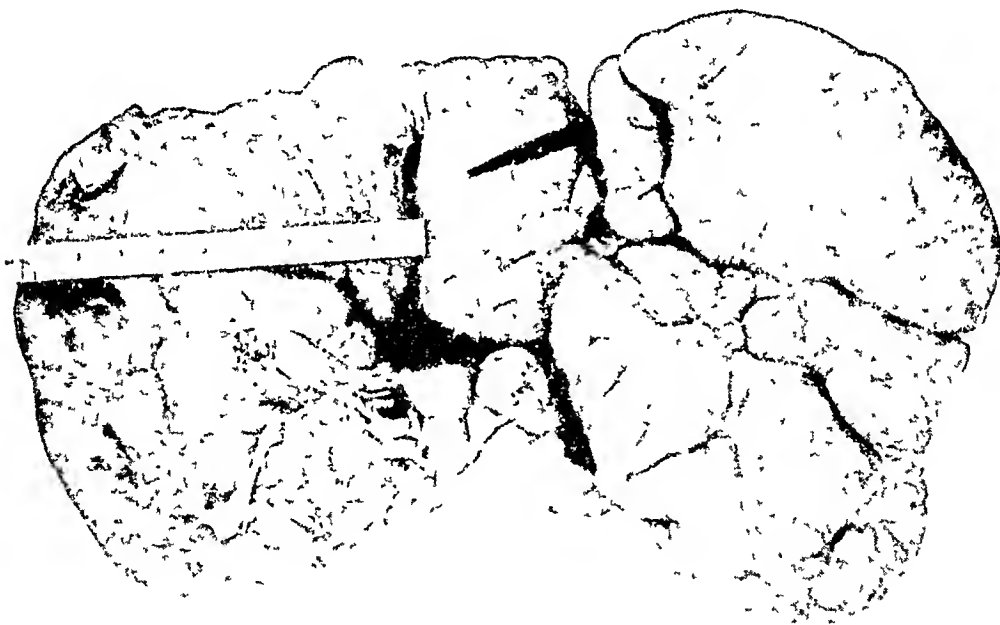


FIG. 4. Inferior surface of liver showing gross lobulation.

The clinical diagnosis was acute bronchopneumonia, pulmonary emphysema, idiopathic steatorrhea and suspected portal cirrhosis.

The patient was placed in an oxygen tent in the orthopneic position. Penicillin, 15,000 units intramuscularly every three hours, was prescribed. A diet high in protein and carbohydrate and low in fat was ordered along with added vitamins A and D. There was an initial slight improvement and decrease in fever. However, after two weeks of this therapy a generalized urticarial reaction developed along with an increase in fever. Penicillin was therefore discontinued. The urticaria cleared quickly, but his general condition grew steadily worse; he became drowsy, took very little nourishment, and expectorated very little sputum, although the cough appeared to be productive. Urobilin was found in the urine in moderate amounts on several occasions, and he developed a slight anemia. There was a progressive fall of serum

albumin and rise of serum globulin, the values on March 26 being total 6.8 per cent, albumin 2.6 per cent, and globulin 4.2 per cent and fractionation at 13.5 per cent sodium sulfite was 1.6 per cent. The Van den Bergh and prothrombin time remained



FIG. 5 (*Above*). Liver showing marked cirrhosis.  $\times 92$ .

FIG. 6 (*Below*). Dilated bile ducts filled with inspissated material.  $\times 110$ .

normal. Systemic penicillin therapy was again instituted on March 17 and continued until shortly before death, without benefit. He became stuporous, more cyanosed and dyspneic, and died on March 30.

*Autopsy Findings:* March 31, 1946 (14 hours after death).

The body was poorly nourished. Thick, greenish purulent material overflowed from the mouth. The ankles and wrists were unduly large and there was pitting edema of both lower extremities and moderate clubbing of the fingers.

Both pleural spaces were obliterated by fibrinous adhesions which were easily broken down. The lungs did not collapse when removed from the chest, but remained distended, as though fixed by inflation. The free margins were pale and feathery on palpation. Numerous diffusely scattered small nodules were felt throughout all lobes. On the cut surface these nodules were found to be grayish-red, circumscribed, consolidated areas surrounding the smaller bronchi, many of which were broken down to form tiny abscesses (figure 1). The bronchi throughout both lungs were dilated in a fusiform manner. The trachea and the whole of the bronchial tree were filled with thick, tenacious, greenish purulent exudate which elung to the mucosa. On culture it grew *Staphylococcus aureus* and *Streptococcus hemolyticus*. The bronchial mucosa had a granular, opaque and congested appearance. Numerous discrete, mod-



FIG. 7. Gall-bladder showing cyst formation.  $\times 170$

erately enlarged tracheal and hilar lymph nodes were found. The most striking microscopic finding was that of extensive, patchy squamous metaplasia of the bronchial epithelium (figure 2). The mucous glands of the large bronchi were distended with mucus. There was extensive bronchiectasis in both lungs, the bronchi being filled with mucopurulent exudate and surrounded by patchy areas of bronchopneumonia, many of which showed early organization. The acute inflammatory process extended into the bronchial walls and in many of these complete breakdown had resulted in communication with small parenchymal abscesses lined by granulation tissue. There were numerous scattered discrete patches of organized alveolar exudate lying in relatively normal lung fields (figure 3). In some areas dilated air sacs typical of emphysema were seen. In other fields the picture was that of pulmonary edema. The visceral pleura was thickened by edema and extremely congested. In some areas the mesothelium was replaced by a fibrinopurulent exudate. The bronchial lymph nodes showed chronic lymphadenitis.

The liver weighed 1,475 grams, was grossly nodular and projected slightly beneath the right costal margin. The largest nodules were on the inferior surface, where they measured up to 4 cm. in diameter (figure 4). The cut surface was of a pale brown color, with a fine fibrous network running throughout the parenchyma. On microscopic examination the portal areas showed extensive irregular fibrosis,



FIG. 8. Pancreas showing replacement of parenchyma by fat.

with proliferation of small bile ducts and slight infiltration by lymphocytes, plasma cells and histiocytes (figure 5). The fine strands of fibrous tissue extended in from the portal areas between the liver cords. In some fields there seemed to be an actual disappearance of parenchyma, with condensation of adjacent portal areas. This was also suggested by the reticulum-stained sections. There were numerous dilated bile



ducts in the portal areas, which were filled with either yellowish bile plugs or masses of eosinophilic, inspissated material (figure 6). There was no real evidence of regeneration of liver tissue. Moderate fatty metamorphosis was present, most marked in the central vein areas. The fat was stained orange with Sudan III.

The gall-bladder was almost empty and was the size of a normal appendix. The lumen contained four small, pale yellow, faceted stones which were embedded in mucus. The wall was thickened. The mucosa of the gall-bladder was a mass of dilated cystic spaces lined by flattened cells and filled with mucus (figure 7). The lining epithelium was remarkably well preserved, probably owing to the complete absence of bile in the lumen. There was no evidence of inflammation. The cystic duct was completely occluded by a stone immediately above the junction with the common bile duct. The common bile duct and the ampulla of Vater were patent.

The wall of the small intestine was thickened and edematous throughout, but more particularly so in the terminal ileum. The large bowel was similarly thickened in the cecum and sigmoid colon, and contained pale yellowish, pasty feces. Microscopic sections from the ileum and colon showed marked thickening of submucosa by edema. Numerous enlarged lymph nodes, similar to the tracheo-bronchial ones, were scattered throughout the mesentery and the region of the pancreas and porta hepatis.



FIG. 9. Remnants of pancreatic tissue surrounded by fat.  $\times 148$ .

The pancreas was of normal or slightly smaller than normal size (figure 8). The cut surface was pale and gelatinous. There was a marked decrease of the usual lobulation. A tiny duct was found which was too narrow to admit an ordinary probe. No communication with the duodenum could be proved and no accessory duct could be found. Numerous sections through the head, body and tail were examined and all showed profound fatty replacement of the acinar elements of the gland. Some sections across the entire width of the gland showed no recognizable acinar tissue. The islets of Langerhans were left as scattered foci of round cells embedded in the fat. There were, however, a few isolated irregular lobules of fairly dense fibrous tissue in which atrophic acini and small ducts could be identified, some of which were slightly dilated (figure 9). There was no evidence of active or chronic inflammation apart from an

occasional lymphocyte. A section stained with mucicarmine showed scattered masses of mucin, both intracellular and within the lumen.

No significant pathological change could be found on examination of the heart, stomach, duodenum, kidneys, spleen, and adrenals. There was no evidence of squamous metaplasia of the epithelium of the renal pelvis which might suggest vitamin A deficiency.

### DISCUSSION

Cystic fibrosis of the pancreas is a disease of infancy and childhood. It is usually manifest clinically by the celiac syndrome accompanied by chronic pulmonary disease, such as bronchiectasis or lung abscess, and a terminal bronchopneumonia.<sup>1, 2, 3, 4</sup> The gastrointestinal symptoms usually appear shortly after birth and consist of passage of large, loose stools, which are often recognized as fatty, distention of the abdomen and intolerance to fat in the diet; under-development follows. Infants living longer than a few weeks develop infection of the respiratory tract.<sup>1, 2, 5, 7</sup> On pathological examination, the pancreas is usually firmer, smaller and thinner than normal. The cut surface shows irregular lobulation with wide bands of connective tissue. Occasionally, however, the pancreas is grossly fatty.<sup>1, 3, 6</sup> Microscopically, the essential lesion is a profound disappearance of acini, replacement fibrosis and variable dilatation of small and large ducts which are filled with inspissated secretion. The term, cystic fibrosis of the pancreas, is derived from these microscopic findings. The islets of Langerhans are not affected. Lesions of the lungs are almost invariably present except in those infants dying during the first week of life.<sup>1, 2, 3, 7</sup> Infants living only a few weeks are found to have bronchopneumonia. Cases of longer duration commonly develop bronchiectasis or abscesses in relation to the smaller bronchi, interstitial fibrosis, pulmonary emphysema and terminal bronchopneumonia. Microscopically, a striking feature in some cases is squamous metaplasia of the bronchial mucosa. The invading organism in the lung is usually the *Staphylococcus aureus*.<sup>1, 7</sup> A fatty liver is a frequent finding and, uncommonly cirrhosis is present.<sup>1, 2, 3</sup> In Anderson's<sup>1</sup> series of 49 cases, 19 showed fatty livers and four cirrhosis.

The above syndrome may be confused with idiopathic celiac disease, the gastrointestinal symptoms of which are similar. However, the latter disease rarely develops before the age of nine months to two years, is not accompanied by chronic pulmonary infection and is seldom fatal. Pathologically, there are no pancreatic lesions.

This patient showed most of the above described features of cystic fibrosis of the pancreas. Steatorrhea had probably been present since shortly after birth. He was underdeveloped and had the pulmonary changes described above. The infecting organisms in the lung were the *Streptococcus hemolyticus* and *Staphylococcus aureus*, the latter being the most frequent invading organism in this disease. The pancreas showed a striking degree of atrophy of the exocrine parenchyma which is a constant finding in this syndrome.<sup>2</sup> The almost complete fatty replacement of the acinar elements with only slight fibrosis, is an occasional finding.<sup>1, 6</sup> It occurred in four of the series of 49 cases reported by Anderson. Microscopic evidence of cystic dilatation of the pancreatic ducts was only slight in our case. There was fatty infiltration and cirrhosis of the liver.

The etiology and pathogenesis of this disease are not known. The fact that the lesions in the pancreas have been found at birth strongly indicates a con-

genital defect in that organ.<sup>1, 2, 3</sup> Partial obstruction of the pancreatic ducts by inspissated secretion may lead to dilatation and atrophy of the ducts and acini, followed by replacement fibrosis. The subsequent development of chronic suppurative in the lungs has not been satisfactorily explained. Anderson<sup>1</sup> suggested that vitamin A deficiency, as a result of defective absorption of this fat soluble vitamin, leads to the squamous metaplasia found in various organs, including the bronchi. Metaplasia of bronchial epithelium with loss of cilia must hinder drainage of lung secretions, thereby predisposing to lung infection. However, lung infection is not common in adult humans or animals with pancreatic duct obstruction.<sup>3</sup> Farber has advanced the theory that body secretions generally are too viscid in this disease and that, in the bronchi and bronchioles, tenacious secretion may lead to a partial obstruction rendering them prone to infection.

The fatty infiltration of the liver is probably the result of the loss of the exocrine pancreatic function. Allan et al.<sup>8</sup> and Fisher<sup>9</sup> have shown that depancreatized dogs developed marked fatty infiltration of the liver, even though they were adequately treated with insulin. Moreover, Ralli et al.<sup>10</sup> and Montgomery et al.<sup>11</sup> produced fatty changes in the livers of dogs, following pancreatic duct ligation, which were indistinguishable from those of depancreatized dogs. A complete explanation for the deposition of fat in the liver under the above experimental conditions cannot be offered at present. But, it has been demonstrated, in the above animals, that the addition of raw pancreas to the diet prevented the abnormal deposition of lipids in the liver.<sup>8, 9, 11</sup> Similarly, Hershey<sup>12</sup> has shown that the oral administration of lecithin has the same effect, and Best et al.<sup>13</sup> have proved that choline, a component of lecithin, is likewise effective. It is possible that the lack of pancreatic juice interferes with the absorption of some dietary constituent which inhibits the deposition of abnormal amounts of fat in the liver.

The cirrhosis of the liver may be the result of prolonged fatty infiltration. Himsworth and Glynn<sup>14</sup> state that in animal experiments, a prolonged heavy fatty infiltration of the liver is an essential precursor and concomitant of diffuse fibrosis. Moreover, Chaikoff et al.<sup>15</sup> in a study of 16 depancreatized dogs maintained on insulin and an adequate diet for periods longer than one year, observed fatty livers in all of the animals, extensive cirrhosis in four, and abnormal fibrosis in another four. The duration of survival in patients dying with cystic fibrosis of the pancreas appears to be an important factor in the development of fatty infiltration and cirrhosis of the liver. In Anderson's<sup>1</sup> series a fatty liver was more frequently met with in children over six months of age and the cases showing cirrhosis varied in age from 17 months to 10 years.

#### SUMMARY

A case of cystic fibrosis of the pancreas in a 17 year old male is presented. The outstanding features are: (a) symptoms suggesting steatorrhea since shortly after birth, (b) underdevelopment, (c) chronic pulmonary suppuration with squamous metaplasia of the bronchial epithelium, (d) cirrhosis of the liver, and (e) the almost complete replacement of acinar elements of the pancreas by fat and fibrous tissue.

A brief review of the literature of this syndrome is described and the etiology and pathogenesis of the lesions are discussed.

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**PARALYSIS DUE TO REDUCED SERUM POTASSIUM CONCENTRATION DURING TREATMENT OF DIABETIC ACIDOSIS: REPORT OF CASE TREATED WITH 33 GRAMS OF POTASSIUM CHLORIDE INTRAVENOUSLY \***

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SHORTLY after the discovery of insulin, Harrop and Benedict observed that insulin administration is followed by a decrease in the concentration of potassium in the serum.<sup>1</sup> Though it had been anticipated by several investigators, 23 years elapsed before Holler reported a case illustrating the possible serious consequences of this relationship in the treatment of diabetic acidosis.<sup>2</sup> Holler noted the development of profound weakness and eventual paralysis of the

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muscles of respiration in the course of treatment of a patient with diabetic acidosis, and demonstrated that this complication was associated with low serum potassium concentration. The administration of potassium salts resulted in dramatic improvement. Holler pointed out certain physiological mechanisms which might have induced the deficiency of serum potassium, and emphasized features which he considered responsible for the severity of the reduction of serum potassium in his patient, namely, the prolonged period of acidosis, the striking diuresis occurring during the period of treatment, and the large doses of glucose and insulin employed.

Nicholson and Branning<sup>3</sup> reported two similar cases, one of whom recovered following the administration of potassium chloride by mouth. Frenckel, Groen, and Willebrands recently described an additional case with recovery following treatment with potassium chloride orally.<sup>4</sup>

In the past year symptoms due to potassium deficiency have been recognized in two cases of diabetic acidosis in this hospital. One of these succumbed, it is believed, as a result of this complication. The other patient is reported in detail below. A feature of this case is the fact that a much larger quantity of potassium salt was administered than has been employed previously, a quantity which we believe more nearly approximates the actual deficiency present.

#### CASE REPORT

A 28 year old married white female was admitted to the Johns Hopkins Hospital at 5:30 a.m., July 21, 1947 in diabetic acidosis. Diabetes had been discovered in May, 1943, when the patient had been admitted to another hospital in coma. The patient repeatedly failed to adhere to her diet or to take insulin regularly, with the result that in the ensuing four years she was admitted to this hospital on seven occasions for various complications of poorly controlled diabetes.

Seven weeks prior to the present admission the patient was discharged from another hospital apparently well controlled on a diet containing protein 100 grams, fat 70 grams and carbohydrate 175 grams, with 35 units of protamine zinc insulin daily. She is alleged to have adhered strictly to this regimen until seven days prior to admission, when she abandoned her diet and omitted insulin for a period of five days. Polyuria recurred, the patient became nauseated, and for at least 36 hours prior to admission vomited repeatedly. On the evening of the fifth day of insulin withdrawal the patient took 35 units of protamine zinc insulin and repeated this dose the following morning. Vomiting continued, the patient became increasingly drowsy, and she was admitted early in the morning of the seventh day in diabetic coma.

Rectal temperature was 97.6° F. The pulse was regular, 120 per minute, blood pressure was 120 mm. Hg systolic and 70 mm. diastolic and the respirations were 28 per minute, Kussmaul in type. The patient was semi-conscious. The breath had the odor of acetone. There was evidence of marked dehydration. The deep tendon reflexes were present though hypoactive throughout. There were no other significant findings on physical examination.

Urinalysis revealed strongly positive reactions for glucose, acetone and diacetic acid. Blood sugar was 560 milligrams per 100 c.c. and the carbon dioxide combining power of the serum was 6.3 milliequivalents per liter (14.0 volumes per cent).

The therapy and course during the first 27 hours in the hospital are presented in table 1. For purposes of discussion the course has been divided arbitrarily into four periods: (1) course prior to potassium therapy, (2) first period of potassium therapy, (3) second period of potassium therapy, (4) third period of potassium therapy.

*Course Prior to Potassium Therapy:* (5:30 a.m. to 2:25 p.m.) Crystalline zinc

TABLE I  
Course and Details of Therapy During First 24 Hours

Time	Therapy	Blood Chemistry				Urine			Remarks	
		Insulin units CZI	Sugar mg. %	CO <sub>2</sub> m.eq./L.	Serum K m.eq./L.	NPN mg. %	Glucose	Acetone		Diabetic Acid
PERIOD I. COURSE PRIOR TO POTASSIUM ADMINISTRATION										
5:30 a.m.	200 c.c. 5% glucose; 100 c.c. saline 500 c.c. plasma	50	560	6.3			4+	3+	Patient admitted in diabetic coma.	
6:00							4+	3+		
7:00		50					4+	3+		
8:00		50					4+	3+		
9:00		{ 1,500 c.c. saline 750 c.c. M/6 Na lactate 200 c.c. 50% glucose	50	508	15.3		57	3+		3+
10:30	{ 1,500 c.c. saline 200 c.c. 50% glucose	50					3+	3+	Shallow respirations noted. EKG evidence of low serum K. Figure 1A.	
11:00							3+	3+		
11:30							3+	3+		
12:00 n							3+	3+		
12:30 p.m.			50	800	13.2	1.8	42	3+		3+
1:30									EKG changes more pronounced. Figure 1B. Gastric lavage. EKG changes extreme. Figure 1C.	
2:00					1.4			3+		3+
PERIOD II. FIRST PERIOD OF POTASSIUM THERAPY										
2:30 p.m.	500 c.c. 0.4% KCl and 0.6% NaCl 500 c.c. 0.4% KCl and 0.6% NaCl 500 c.c. 0.4% KCl and 0.6% NaCl 500 c.c. 0.4% KCl and 0.6% NaCl								Complete flaccid quadriplegia. Definite improvement in EKG. Marked improvement in EKG. Paralysis subsiding.	
3:00										
3:30								3+		2+
4:00										1+

PERIOD III. SECOND PERIOD OF POTASSIUM THERAPY									
4:30 p.m.	{ 1,000 c.c. 10% glucose 1,000 c.c. 10% amigen 5 gm. KCl	50	280	16.1	2.7	3+	1+	0	EKG evidence of further reduced serum K. Bigeminal rhythm. Recurrence of flaccid quadriplegia.
5:30						4+	1+	0	
5:30						4+	1+	0	
6:30					1.56	4+	1+	0	Progressively weaker.
7:30									Gastric dilatation. 1,500 c.c. removed. EKG indicates further reduction in serum K.
9:00	500 c.c. saline								
9:30									
PERIOD IV. THIRD PERIOD OF POTASSIUM THERAPY									
10:00 p.m.	{ 1,000 c.c. saline 500 c.c. 2% KCl	25			2.1	3+	0	0	Immediate clinical improvement. EKG improved.
10:30						3+	0	0	
11:30	{ 1,500 c.c. saline 5 gm. KCl								
12:30 a.m.		25				3+	0	0	Sustained improvement in muscular strength.
3:00 a.m.	{ 250 c.c. saline 500 c.c. 5% glucose 250 c.c. 2% KCl		368	23.3	2.2	1+	0	0	
6:00 a.m.	I-V fluids discontinued	25							Sustained clinical improvement.
8:30 a.m.			152	16.1	2.4	1+	0	0	Able to sit up and eat.

For convenience, times are indicated to the closest half hour.

insulin was given hourly in doses of 50 units. Fluids were administered as a continuous intravenous infusion, as shown in table 1. The urine output during the period was 4,000 cubic centimeters. During this period 37 milliequivalents of potassium were excreted in the urine. She was given 650 cubic centimeters of water orally. A gastric lavage with 5 per cent sodium bicarbonate solution was performed. No gastric contents were obtained, and approximately 500 c.c. of the bicarbonate solution were left in the stomach. It is perhaps well to state that the above treatment is a considerable variation from the standard therapy of diabetic acidosis customarily employed in this clinic.

Four hours after admission it was noted that the patient's respirations had become rapid and shallow. The sensorium had cleared considerably, and the patient responded well. There was no dyspnea. The pulse rate was 120, and the blood pressure was 130/80. Ocular movements were performed normally, and there was no disturbance of speech or difficulty in chewing or swallowing. There was, however, marked weakness of the muscles of all four extremities and to a lesser extent of the neck muscles. Tendon reflexes were now absent throughout. There was no impairment of sensation.

The development of profound muscular weakness suggested the possibility of low potassium concentration in the serum. An electrocardiogram taken five hours after admission revealed sagging of the S-T segments and low amplitude of the T-waves in all leads (figure 1A). Serum potassium six hours after admission was 1.8 milliequivalents per liter. The electrocardiogram taken at this time showed further changes (figure 1B). Two hours later the potassium was further reduced to 1.4 milliequivalents per liter, and there were even more striking changes in the electrocardiogram (figure 1C). Meanwhile the patient became progressively weaker. Seven hours after admission muscle strength as measured by a dynamometer (Stoeltzing) was only nine kilograms in the right hand and eight kilograms in the left hand (normal, female, 20 to 30 kilograms). Thirty minutes later dynamometer readings were six kilograms in the right and five kilograms in the left hand.

*First Period of Potassium Therapy:* (2:25 p.m. to 4:20 p.m.) Nine hours after admission insulin and glucose were discontinued, and over the subsequent two hours the patient was given intravenously 2,000 cubic centimeters of a solution containing 0.4 per cent potassium chloride (54 milliequivalents of potassium per liter) and 0.6 per cent sodium chloride in distilled water. Two grams of potassium citrate were given orally during the first half hour. An electrocardiograph with a Sanborn cardio-scope attachment was connected to the patient throughout the period of therapy. This permitted constant observation of the electrocardiographic changes and facilitated the taking of electrocardiograms at frequent intervals.

The potassium chloride solution was administered at a rate of 18 to 20 cubic centimeters per minute. Definite regression of the electrocardiographic abnormalities was observed within 10 minutes (figure 2A). Twenty-five minutes after beginning the infusion the patient had received 500 cubic centimeters of the solution (2.0 grams of potassium chloride or 27 milliequivalents of potassium) and further improvement was noted in the electrocardiogram (figure 2B). There was, however, no corresponding improvement in the clinical condition of the patient. In fact, she complained of numbness and tingling in both hands, and examination revealed a flaccid paralysis of both arms and legs. She was unable to raise or turn the head from side to side. Respirations were almost entirely diaphragmatic with hardly discernible excursions of the chest. There were, however, no complaints of dyspnea nor evidence of oxygen lack at any time. Speech, mastication, deglutition, ocular and facial movements were grossly unimpaired. The patient was able to move the toes of both feet only slightly. Deep tendon reflexes were unobtainable, and the plantar reflexes were absent. Sensation to pinprick and cotton wool was intact.



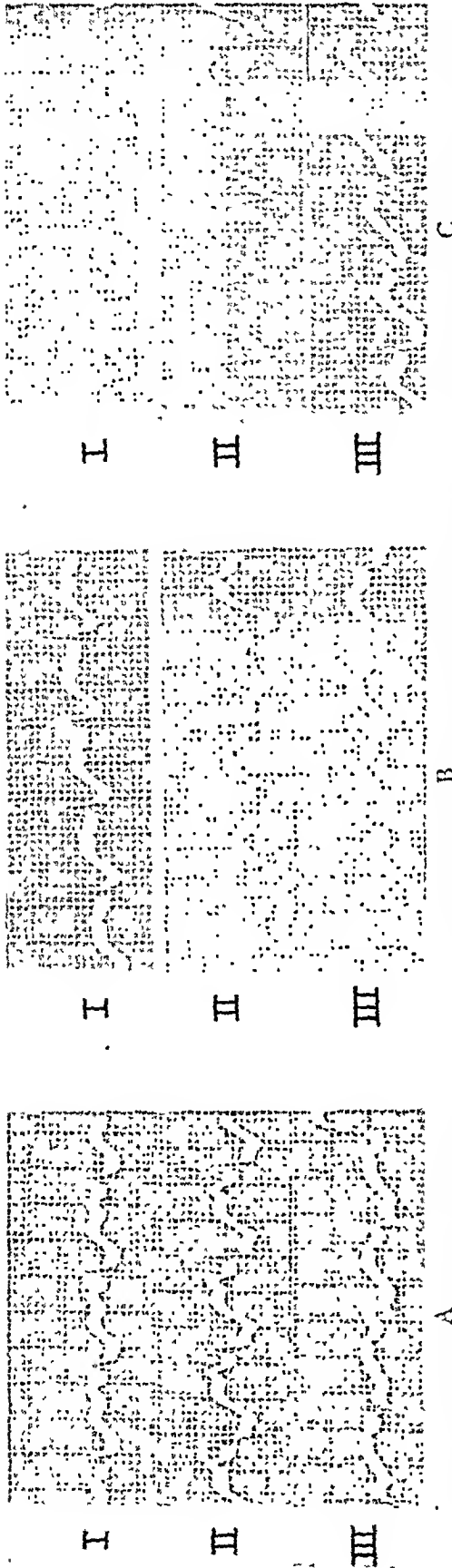


FIG. 1. Electrocardiograms prior to administration of potassium. Note depression and sagging of ST segments characteristic of low serum potassium. A. 11:00 a.m. Five and one-half hours after admission. Serum K at 11:55 a.m.: 1.8 m.eq. per L. B. 12:50 p.m. C. 2:15 p.m. Serum K at 2:10 p.m. 1.4 m.eq. per L.

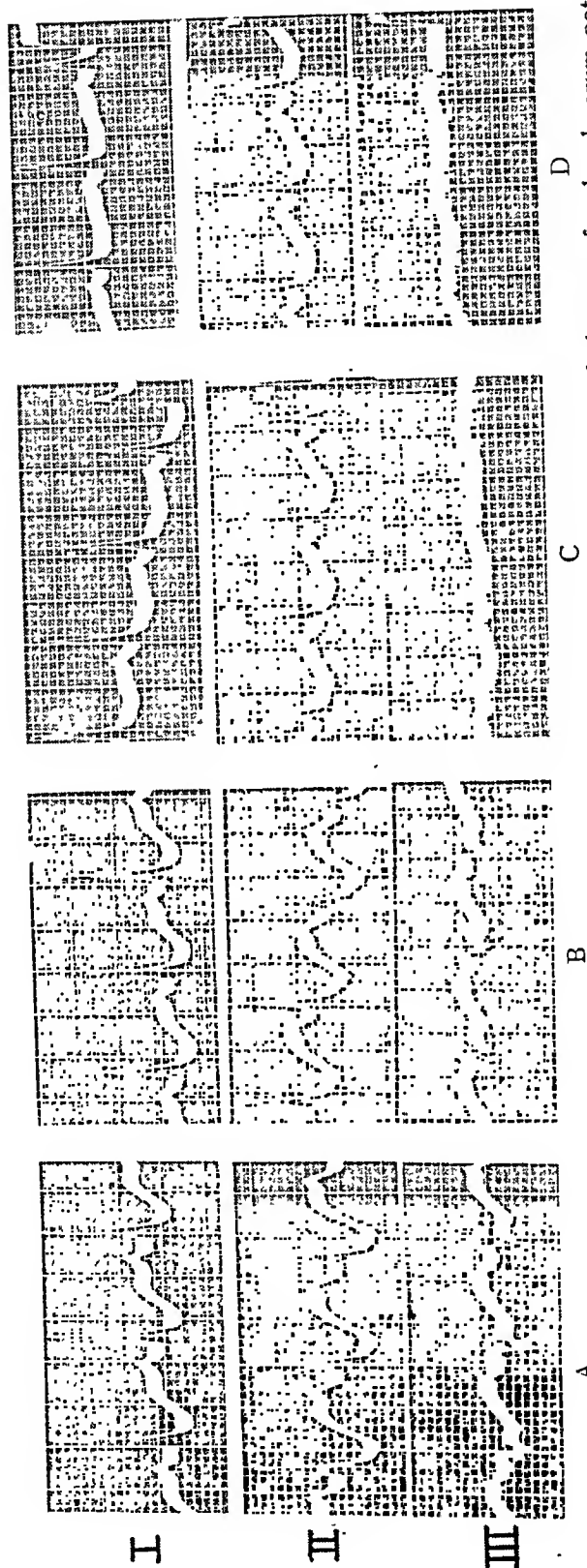


FIG. 2. Electrocardiograms during the first period of potassium therapy. Note gradual regression of changes of reduced serum potassium. *A.* 2:35 p.m. Ten minutes after beginning 0.4 per cent KCl intravenously. *B.* 2:50 p.m. After 2.0 gm. KCl intravenously and 2.0 gm. K citrate orally. *C.* 3:25 p.m. After 4.0 gm. KCl intravenously and 2.0 gm. K citrate orally. *D.* 3:55 p.m. After 6.0 gm. KCl intravenously and 2.0 gm. K citrate orally. Serum K at 4:20 p.m.: 2.7 m.eq. per L.

Potassium therapy was continued at approximately the same rate, and there occurred a gradual return of muscle power. Eight grams of potassium chloride were administered intravenously and 2.0 grams of potassium citrate were given by mouth during the two hour period, at the end of which the patient was remarkably improved. Respirations were deeper, and the arms and legs could be moved without difficulty. The paresthesias of the arms slowly subsided. Electrocardiograms showed gradual progress toward normal (figure 2C, D). At the end of the period the serum potassium concentration was 2.7 milliequivalents per liter. The blood sugar was 280 milligrams per cent, the serum carbon dioxide combining power was 16.1 milliequivalents per liter. Urinalysis showed a three plus qualitative test for glucose, a trace of acetone, and no diacetic acid. No glucose or insulin was given during this two hour period.

*Second Period of Potassium Therapy:* (4:20 p.m. to 9:40 p.m.) There was now begun an intravenous infusion of a mixture containing 2,000 cubic centimeters of water, 100 grams of Amigen, 100 grams of glucose and 5 grams of potassium chloride. This was administered at an average rate of 8 cubic centimeters per minute. The Amigen itself contained 4.5 milliequivalents of potassium. The 2,000 cubic centimeter solution, therefore, contained 5.33 grams of potassium chloride (72 milliequivalents of potassium). Fifty units of crystalline zinc insulin were given subcutaneously at the beginning of this period.

Within 30 minutes an electrocardiogram showed return of the changes associated with a fall in serum potassium (figure 3A). Shortly after this, bigeminal rhythm was observed (figure 3B). The apical rate was approximately 120 per minute with a pulse deficit of 60 per minute. The ectopic beats could be abolished temporarily by pressure on the right carotid sinus but the arrhythmia immediately recurred (figure 3B). The patient became steadily weaker, and at the end of one and one-half hours again exhibited a complete flaccid quadriplegia. Three hours after beginning the Amigen-glucose-potassium mixture and the accompanying injection of insulin, the serum potassium had fallen to 1.56 milliequivalents per liter. The 2,000 c.c. glucose-Amigen-potassium chloride mixture was given over a period of four hours and 20 minutes at the conclusion of which the infusion was continued by the addition of 500 c.c. of 0.85 per cent sodium chloride solution. Gastric dilatation was recognized during this period and was relieved by the removal of 1,500 cubic centimeters of thick green fluid from the stomach. Following this the bigeminal rhythm disappeared and the electrocardiogram showed still more pronounced changes indicative of low serum potassium (figure 3C). The quadriplegia persisted.

*Third Period of Potassium Therapy:* (9:40 p.m. to 6:00 a.m.) In view of the recurrence of paralysis together with the evidence of further decrease in the level of serum potassium, potassium chloride was administered at a more rapid rate: 500 cubic centimeters of a 2 per cent solution of potassium chloride were added to 1,000 cubic centimeters of 0.85 per cent sodium chloride and given by continuous intravenous infusion. This solution containing 10 grams of potassium chloride (135 milliequivalents of potassium) was given over a period of two hours. Improvement in the electrocardiogram was apparent within 10 minutes (figure 4A). Within 30 minutes the patient was remarkably improved. She could once again move the extremities, though muscular weakness was evident and tendon reflexes were still absent. The serum potassium concentration 50 minutes after adding the potassium chloride solution was 2.1 milliequivalents per liter. At the termination of this infusion the patient was vastly improved and an electrocardiogram showed further change toward normal (figure 4B).

During the subsequent six and one-half hours an additional 10 grams of potassium chloride were administered intravenously, as shown in table 1. There was gradual improvement in muscle strength. No further changes of significance were noted in

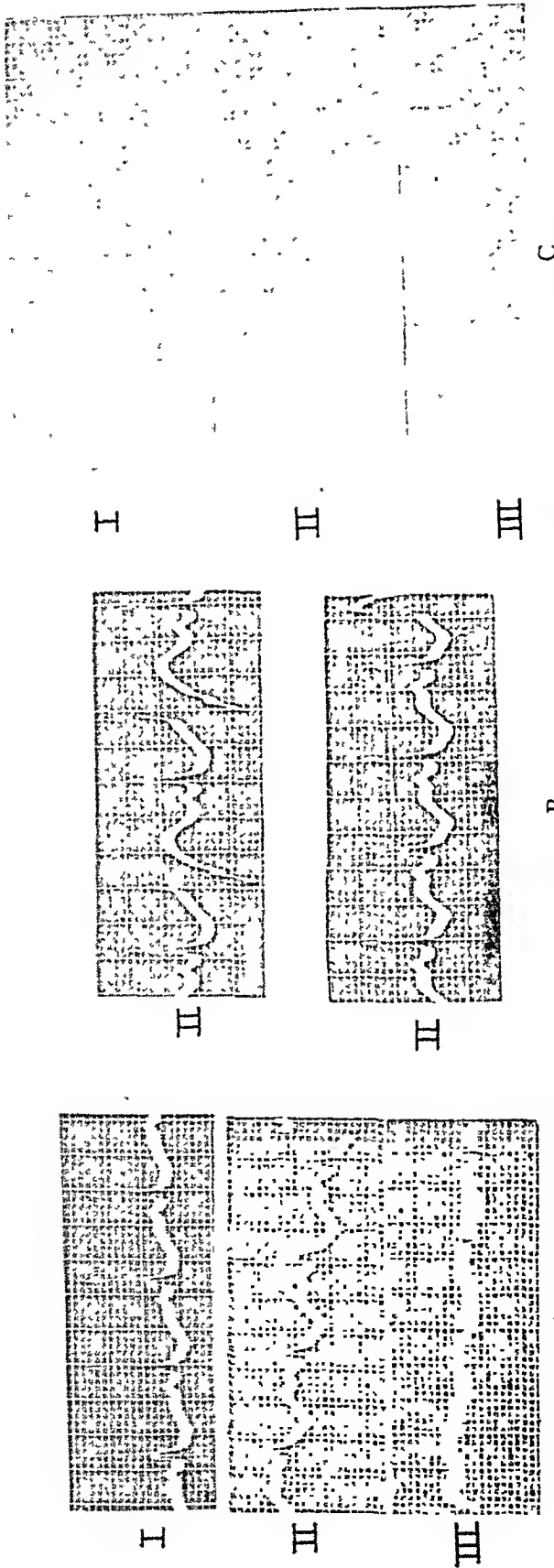


FIG. 3. Electrocardiograms during the second period of potassium therapy. Note reappearance of changes indicative of reduced serum potassium. *A.* 5:00 p.m. Thirty minutes after 50 units of insulin and beginning 10 per cent glucose-Amigen-potassium solution. *B.* 6:05 p.m. One and one-half hours after beginning the above therapy. Bigeminal rhythm has appeared (upper record) which reverts temporarily to normal rhythm following carotid sinus pressure (lower record). Lead II only. *C.* 9:25 p.m. Five hours after beginning above therapy at completion of 1000 c.c. 10 per cent glucose, 1,000 c.c. 10 per cent Amigen and 5.0 gm. KCl intravenously. Serum K at 8:30 p.m.: 1.6 m.eq. per L.

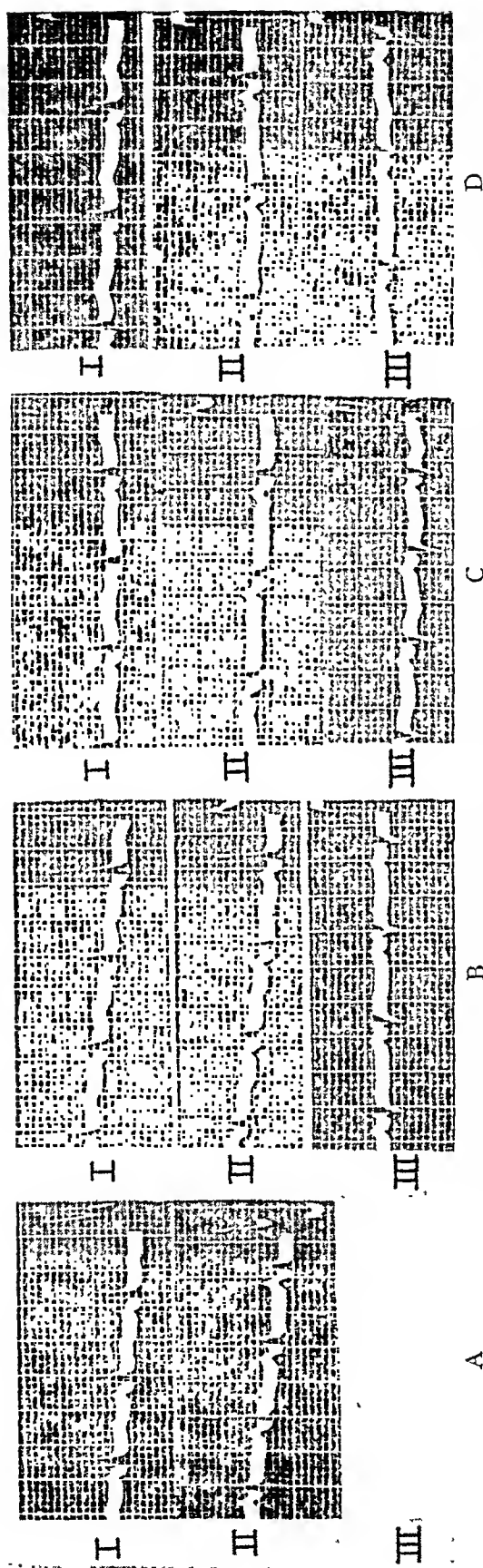


Fig. 4. Electrocardiograms during the third period of potassium therapy. Note the prompt regression of electrocardiographic changes of marked reduction of serum potassium concentration. A. 9:45 p.m. Five minutes after beginning 0.66 per cent KCl solution intravenously. B. 11:30 p.m. Following 10.0 gm. KCl intravenously in previous 1.8 hours. C. 2:30 a.m. Following 15.0 gm. KCl during previous five hours. Serum K at 3:00 a.m.: 2.2 m.eq. per L. D. 8:00 a.m.: 2.4 m.eq. per L. At conclusion of potassium therapy. Serum K at 8:00 a.m.: 2.4 m.eq. per L.

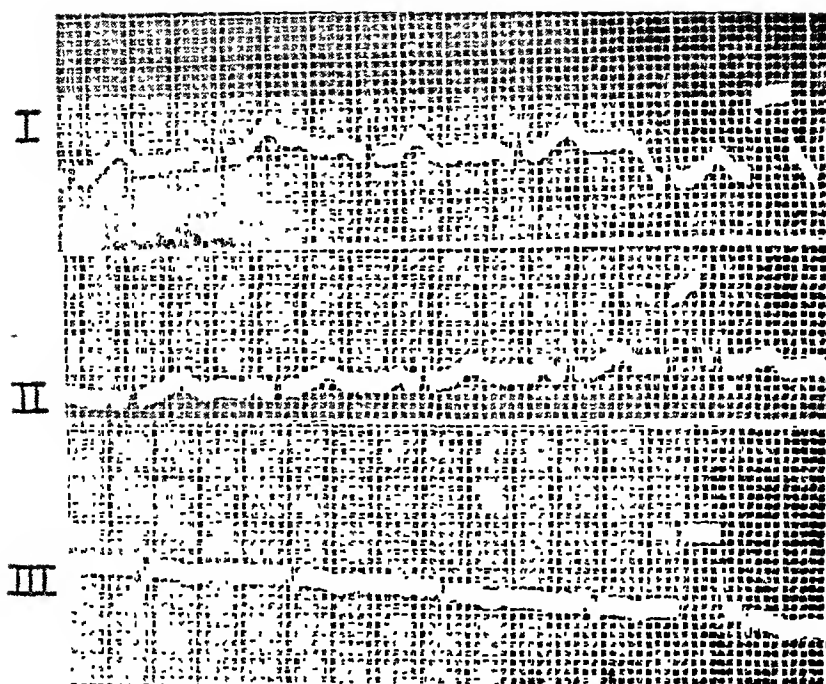


FIG. 5. Electrocardiogram on third hospital day. Normal electrocardiogram. Serum K at this time: 3.3 m.eq. per L.

the electrocardiograms (figure 4C, D). Intravenous therapy was discontinued 24 hours after admission at which time the patient was able to move about and feed herself without difficulty. Blood studies 27 hours after admission gave the following results: serum potassium 2.4 milliequivalents per liter, blood sugar 152 milligrams per cent, serum carbon dioxide combining power 16.1 milliequivalents per liter, serum chloride 109.5 milliequivalents per liter.

The remainder of the hospital course was without incident except for development of a mild urinary tract infection. The patient was able to take a full diet by mouth beginning at noon on the second day in the hospital. The daily potassium intake was calculated and the level of serum potassium determined each morning (table 2). It will be noted that the serum potassium did not reach normal levels until the fifth hospital day. An electrocardiogram on the third hospital day was normal (figure 5).

TABLE II  
Serum Potassium Levels During Recovery from Diabetic Acidosis

Date	Daily Oral Intake of Potassium	Serum Potassium Level
7-23-47	3.1 gm. (79.0 m.eq.)	3.3 m.eq./L. (9:30 p.m.)
7-24-47	3.8 gm. (96.9 m.eq.)	3.3 m.eq./L. (8:30 a.m.)
7-25-47	3.7 gm. (94.3 m.eq.)	3.8 m.eq./L. (8:30 a.m.)
7-26-47	4.0 gm. (102.0 m.eq.)	3.95 m.eq./L. (8:30 a.m.)
7-27-47	Not calculated (diet unchanged)*	3.5 m.eq./L. (8:30 a.m.)
7-28-47	Not calculated (diet unchanged)*	4.1 m.eq./L. (8:30 a.m.)
7-29-47	Not calculated (diet unchanged)*	4.8 m.eq./L. (8:30 a.m.)
7-30-47	Not calculated (diet unchanged)*	3.8 m.eq./L. (8:30 a.m.)
7-31-47	Not calculated (diet unchanged)*	Not determined
8- 3-47	Not calculated (diet unchanged)*	4.6 m.eq./L. (8:30 a.m.)

\* Throughout this period the patient was given a normal diet containing protein 100 gm., fat 70 gm., and carbohydrate 175 gm. Calculations were made by Miss Janette C. Carlsen, chief ward dietitian, Osler Medical Clinic. Calculations were based on actual food intake and standard tables (Sherman, H. C.: Chemistry of Food and Nutrition, 7th Edition, 1946, New York, Macmillan Company).

In the light of the events described above, the previous hospital admissions of this patient are of interest. The patient was admitted for diabetic acidosis on three occasions in 1944 and 1945. On two of these admissions the acidosis was treated by the method then customarily employed in this clinic, which consisted of accomplishing the initial hydration by the use of intravenous isotonic sodium chloride and sodium lactate solutions without administration of glucose until the blood sugar had fallen to moderate hyperglycemic levels. During the second admission in October, 1944, however, the patient was treated by a method similar to that employed during the present admission, i.e., by the immediate administration of glucose together with normal saline. Treatment during the first 12 hours consisted of 210 units of crystalline zinc insulin and a total of 7,500 cubic centimeters of fluid intravenously containing 150 grams of glucose.

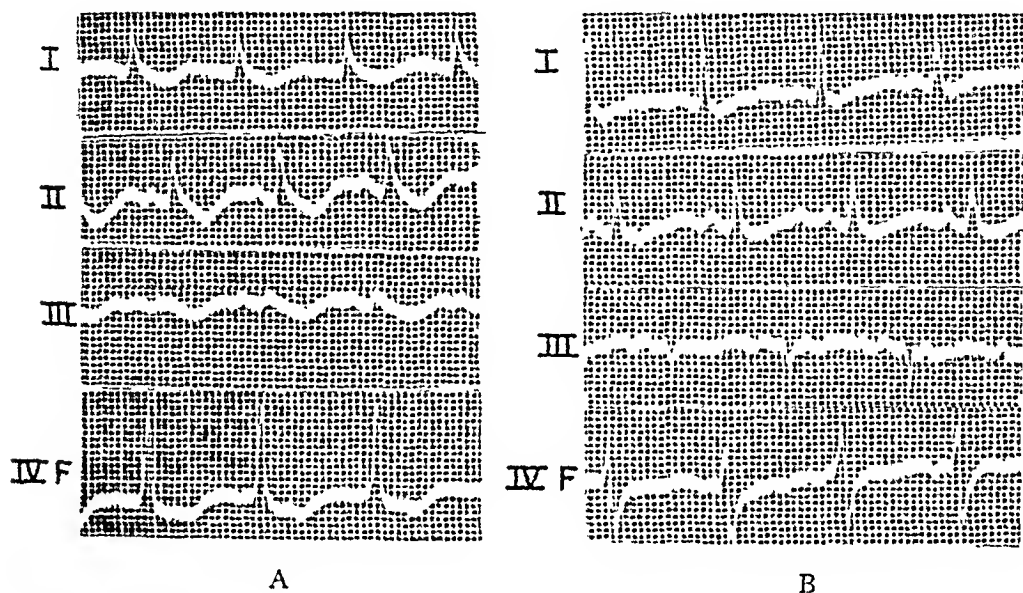


FIG. 6. Electrocardiograms during previous admission for diabetic acidosis. During this admission treatment consisted of large quantities of insulin and glucose. *A*. 24 hours after admission. *B*. 72 hours after admission.

Because of protracted vomiting, intravenous therapy was continued throughout the first two and one-half days in the hospital. The clinical course was satisfactory, but review of electrocardiograms taken on the second and fourth days of that admission indicate the presence of low serum potassium (figure 6A, B).

### DISCUSSION

Paralysis associated with reduced serum potassium concentration is an uncommon but serious complication of therapy of diabetic acidosis.<sup>2, 3, 4</sup> Some reduction in serum potassium is frequently present during treatment of diabetic acidosis, but hypokalemia of the degree exhibited by this patient is rarely encountered.<sup>5, 6</sup> The neurologic manifestations, consisting of progressive muscular weakness and finally flaccid paralysis of the extremities, are similar to those seen in familial periodic paralysis.<sup>7</sup> The correlation between neuromuscular dysfunction and reduction in serum potassium concentration in these two conditions has been pointed out by previous writers.<sup>2, 3, 4</sup>

The syndrome is easily recognized. In the patient reported here the paralysis was limited to the musculature of the extremities and trunk, the cranial nerves being little affected. Breathing was extremely shallow and the respiratory rate

increased, but there was never any dyspnea, nor were there signs of oxygen lack. In the case reported by Holler, respiratory embarrassment was perhaps the outstanding feature. Nicholson and Branning described respiratory difficulties in two patients, one of whom also had difficulty in swallowing.

The physiological mechanisms responsible for the reduction in serum potassium concentration in these instances will be mentioned only briefly. The dehydration which characterizes diabetic acidosis results from the loss of both intracellular and extracellular water. Potassium is lost from the cells with water and is excreted in large quantities in the urine.<sup>11</sup> The concentration of potassium in the extracellular fluid, however, remains normal or may be slightly elevated. The administration of insulin produces a reduction in serum potassium concentration in both normal and diabetic individuals.<sup>1</sup> The administration of large amounts of glucose has a similar effect.<sup>8</sup> This reduction in serum potassium has been shown to be the result of movement of potassium from the extracellular fluid into the tissue cells in the company of glucose—a normal response to increased glycogen formation.<sup>9, 10</sup>

In diabetic acidosis, even after the institution of insulin and glucose therapy, some patients continue to excrete large quantities of potassium in the urine.<sup>12</sup> During the nine hour period prior to potassium therapy, our patient excreted 37 milliequivalents of potassium in the urine. This loss is sufficient to account for a marked reduction in the potassium content of the extracellular fluid if there were no more potassium added from other sources. Thus, if insulin retards the movement of potassium from the cells to the extracellular fluid, and potassium continues to be excreted in the urine, the potassium in the extracellular fluid may fall to dangerously low levels. More detailed studies will be required to describe with accuracy the electrolyte exchanges and renal mechanisms involved.

The administration of large amounts of glucose may be a factor in the production of hypokalemia. It is possible that the diuresis secondary to hyperglycemia in this situation produces an increased urinary excretion of potassium. It seems significant that four of the five instances of paralysis associated with low serum potassium occurred in patients treated with liberal amounts of glucose.

In order to avoid the dangerous complication seen in this patient, it is necessary to recognize early the development of hypokalemia and to institute therapy at once. The greatest fall in serum potassium occurs during the first 24 hours. Certain features common to the cases of paralysis thus far reported should, when encountered, lead one to anticipate this complication. These are: a history of poorly controlled diabetes, a prolonged period of acidosis precipitated by the withdrawal of insulin, the use of large quantities of glucose intravenously, and the excretion of a large volume of urine during treatment.

In situations where potassium determinations are not readily available, the electrocardiogram provides a convenient method for detecting the presence of low levels of serum potassium. The electrocardiographic changes in this patient were quite specific and sufficiently striking to enable clinicians to make the diagnosis of hypokalemia prior to its confirmation in the chemical laboratory. It should be noted that diagnostic alterations were seen only after there had been a fall in serum potassium to levels below 2.5 milli-equivalents per liter. Important from the point of view of therapy is the fact that the changes were recognizable well in advance of the development of paralysis and respiratory



difficulty. Repeated cardiographic observations were invaluable throughout the course in estimating the response to therapy.

The outstanding electrocardiographic changes are seen in the ST segment and T-waves. The earliest change noted is reduced amplitude in the T-waves. With more marked reduction in serum potassium there is striking sagging of the ST segments below the isoelectric lines. The changes observed in this case are similar to those reported by previous writers.<sup>2, 15, 16, 17, 18</sup> In the presence of organic heart disease, digitalis administration, or other complicating electrolyte abnormalities, the interpretation of the cardiographic changes may become more difficult.

A considerably greater amount of potassium was administered to this patient than was employed in the previously reported cases. Holler gave 5.5 grams of potassium chloride intravenously and 4 grams of potassium citrate by mouth. Nicholson and Branning's treatment consisted of 3.6 grams of potassium chloride orally. Frenckel and his associates obtained good results with 4 grams of potassium chloride by mouth. Our patient responded initially to 8.0 grams of potassium chloride by vein, but suffered a relapse following subsequent glucose and insulin therapy despite the addition of potassium chloride to the intravenous infusion.\* A total of 33.3 grams of potassium chloride was administered in the course of 15.5 hours. Even this amount was not sufficient to raise the serum concentration to normal. During the period of potassium therapy, 73 milliequivalents of potassium (equivalent to less than six grams of potassium chloride) were lost in the urine and vomitus. Though the amount of potassium administered seems large, it is of the same order of magnitude as the deficit that has been shown to occur in some cases of diabetic acidosis.<sup>11</sup> In this case, potassium was given intravenously in solutions containing from 0.25 per cent KCl (36 milliequivalents per liter) to 0.66 per cent KCl (90 milliequivalents per liter), at rates varying from 1 gram to 8 grams of potassium chloride per hour.

In the cases reported thus far, the administration of potassium has been employed as an emergency measure to combat the serious effects of reduced serum potassium. It would appear reasonable to administer potassium salts early in the course of therapy of diabetic acidosis as a prophylactic measure. The administration of potassium salts is not without danger, however. Too rapid intravenous injection may result in abnormally high concentrations producing heart block and cardiac standstill.<sup>10</sup> The administration of potassium salts is especially hazardous when renal function is impaired and should never be employed until an adequate urine flow has been assured.<sup>13, 14</sup> Detailed studies are needed to outline the criteria and indications for the use of potassium salts prophylactically in diabetic acidosis.

#### SUMMARY

1. A case of paralysis associated with reduced serum potassium concentration occurring during treatment of diabetic acidosis is reported.
2. The amount of potassium administered to this patient is considerably greater than amounts previously employed in this condition.
3. It is important to anticipate the development of hypokalemia and, when it occurs, to institute treatment promptly in order to avoid the serious effects of marked reduction in serum potassium levels.

\* What effect, if any, the administration of protein hydrolysate may have exerted is not clear.

4. The electrocardiogram offers a rapid and convenient method for the detection of reduced serum potassium concentration and is valuable as a guide to therapy when potassium salts are employed.

The author is indebted to Dr. J. E. Howard for assistance in the preparation of this paper and for permission to use balance data on this patient.

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## SPOROTRICHOSIS, A PROTEAN DISEASE: WITH REPORT OF A DISSEMINATED SUBCUTANEOUS GUMMATOUS CASE OF THE DISEASE \*

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DISEASES for which there exists a specific therapeutic agent are not numerous. Sporotrichosis alone, of all the deep mycoses, belongs in this unique category, which implies that a positive diagnosis of such an infection is tantamount to a significant and worthwhile therapeutic accomplishment. Fewer than 200 cases of sporotrichosis, many of these not verified, had been recorded in this country by 1932.<sup>1</sup> Since that time, however, the proved incidence of the disease has mounted with such rapidity that it now constitutes a disease to be reckoned with on occasion by physicians in every branch of medicine.

Within the genus *sporotrichum* are several species, most of which are not of clinical significance. *S. schenckii* and *S. beurmanni* are those isolated with greatest frequency from human infections, the former being most prevalent as a cause of disease in America.<sup>2</sup> The organism grows well aerobically at room temperature on such a simple medium as Sabouraud's dextrose agar. Within seven to 10 days the colony is apparent as a white aerial growth which gradually becomes conipact and convoluted resembling, according to one observer, worm casts in the sands of the seashore.<sup>3</sup> After a few weeks it is darkly pigmented. If material for inoculation is obtained from secondarily infected lesions there is sometimes an over growth of bacterial contaminants. Incorporation of 50 units of penicillin in the culture medium of each tube or Petri dish will, however, inhibit the growth of a majority of such contaminants, and not interfere materially with growth of the fungus. Culture mount demonstrates an abundance of fine mycelium with numerous short lateral branches supporting pyriform microconidia in such a manner that resemblance to the petals of a flower is often striking. Direct examination of material from which the organism can be cultured with facility seldom reveals the parasite. It is equally as difficult to discern in biopsy specimens although a method has been described which in the experience of the author<sup>4</sup> has proved a valuable aid in detection of the organism in pus and tissues.

Under most circumstances a fungus of low virulence, the sporothrix doubtless requires suitable soil for its rôle as a pathogenic agent, the disease sporotrichosis probably developing in most instances because of a lessened resistance of the host at the time of inoculation.<sup>5</sup> The fungus is exceptionally hardy and is known to thrive in all parts of the world, often as a saprophyte on plants, flowers, grasses and vegetables. Its occurrence in the normal human pharynx and gastrointestinal tract has been adequately verified as has also its ability to permeate the intact intestinal mucosa. It is more than probable that in the latter situation the organism is carried through the intestinal wall by migratory phagocytes.<sup>5</sup> The inoculation by infected vegetable matter of a broken area of skin or mucous membrane is doubtless the mode of infection in most cases of human sporotrichosis, considerable attention having been devoted to the disease

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as an occupational dermatosis.<sup>6</sup> At least two investigators have been infected while working with cultures of the organism and it has been shown that individuals may acquire this mycosis subsequent to the handling of dressings from patients with the disease.<sup>1</sup> Less common sources of infection cited by various authors have been those reputedly acquired from horses and from the bite of a rat, gopher, white mouse, parrot and hen.<sup>5</sup> Some cases of sporotrichosis in France were believed to have occurred subsequent to various intradermal tests.<sup>7</sup> Of considerable interest is the observation that involution of pharyngeal lesions of sporotrichosis may be followed by continued presence of the organism as a saprophyte, rendering the patient a typical "carrier".<sup>1</sup> Occurrence of the disease following cutaneous inoculation of an abrasion by means of the saliva of such a "carrier" has been recorded.<sup>5</sup>

### CLINICAL ASPECTS OF THE DISEASE SPOROTRICHOSIS

A previous observation<sup>5</sup> regarding the clinical polymorphism exhibited by sporotrichosis is an apt one, this feature occasionally being of diagnostic import, especially as regards lesions of the skin. Although the disease is usually divided, for purposes of description, into the cutaneous and systemic types, it is worthy of note that a preponderance of all cases demonstrate involvement of the integument to a variable degree and that demonstrable visceral lesions are most unusual.<sup>8</sup>

When the skin is involved the infection is practically always primary there.<sup>1</sup> The localized lymphangitic type, with a primary lesion at the site of inoculation about the hands or feet, not infrequently simulating a syphilitic chancre, is the variety seen most often in America. It is usually accompanied by an ascending, relatively indolent and painless lymphangitis and few or several gummatous lesions resembling the primary sore and arranged in linear fashion along the course of the involved lymphatics. Palpable regional adenopathy is infrequent and the disease most often remains localized to the involved extremity.

Multiple disseminated subcutaneous gummatous sporotrichosis is encountered frequently in France, though rarely in this country. It is characterized by the occurrence of small, firm, painless subcutaneous nodules, often widely distributed, the lesions softening in their central portion, with eventual production of a miniature life buoy-like structure if the contents are evacuated. These involute after a few weeks or months, only to be succeeded by further crops of similar lesions. On occasion this type of the disease is manifested by an agglomeration of polymorphous lesions which pose a difficult problem in diagnosis.

Systemic sporotrichosis may occur subsequent to dissemination of the disease from a primary cutaneous lesion or lesions, although more frequently it is not possible to demonstrate with certainty a primary focus. Involvement of conjunctival, nasal, lingual, pharyngeal, oral, laryngeal and intestinal mucous membranes has been noted. Gastrointestinal sporotrichosis, however, is exceedingly rare.<sup>1</sup> Osseous lesions are not infrequent and may simulate those of syphilis. Muscular, lymph node and articular involvement has been recorded on several occasions. Cerebrospinal sporotrichosis is for practical purposes a non-entity and the same is true of the pulmonary variety of the disease, one investigator having found only two cases in the entire literature where evidence of the latter type of involvement was at all convincing.<sup>8</sup> A most unusual example of sporotrichosis

accompanied by lesions of the skin, spleen, liver, kidneys, myocardium, adrenals, cerebral cortex and bone marrow has recently been recorded.<sup>9</sup>

Sporotrichosis of itself seldom evokes significant symptomatology. General health is not altered unless and until the process continues untreated for a long period of time, after which intervening infection may complicate the issue and eventuate in a fatal outcome. As with others of the deep mycoses, sporotrichosis has little if any tendency to spontaneous involution and may persist for years if the correct diagnosis is not made and appropriate therapeutic measures instituted.

### DIAGNOSIS

Although demonstration of the causative organism, usually by cultural methods as previously described, is a prime requisite for a positive diagnosis of sporotrichosis, the skin test may on occasion be helpful. The antigen, known as sporotrichin, is injected intracutaneously, the test being read after 48 hours. If it is negative, this mycosis can be eliminated from the realm of diagnostic possibilities. A positive reaction is of considerably less significance and may indicate presence of the disease in question, that the person under consideration is a so-called "carrier" or be merely a cross reaction produced by another mycosis. Animal inoculation is seldom a pre-requisite to the diagnosis of sporotrichosis although intraperitoneal injection of infected material produces a sporotrichotic orchitis in the white rat which may evolve even more rapidly than cultures of the organism. The histopathology of sporotrichosis is usually neither distinctive nor diagnostic, being granulomatous in character, and detection of the fungus in microscopic sections is not a frequent occurrence.

The differentiation of sporotrichosis from other diseases is usually accomplished with ease, but on occasion may tax the diagnostic acumen of the ablest physician. Syphilis and tuberculosis are probably simulated most often, although sporotrichosis occasionally mimics pyogenic infections and other lesions of mycotic origin, notably those of blastomycosis, actinomycosis, coccidioidomycosis and histoplasmosis. A protracted illness, which is accompanied by indolent cutaneous or subcutaneous gummatous lesions having a distribution suggestive of lymphatic dissemination but without the usual inflammatory signs of a coccal infection, and which has failed to respond to ordinary surgical procedures<sup>5</sup> warrants thorough investigation and study as to the possibility of the disease being sporotrichosis. The acknowledged rarity of visceral sporotrichosis is of considerable import in the differential diagnosis of abstruse internal lesions and is for reasons previously cited, of practical significance to the roentgenologist confronted with an obscure pulmonary lesion suspected of being mycotic in origin.<sup>8</sup>

### TREATMENT

In contradistinction to others of the deep mycoses, cases of sporotrichosis respond almost without exception to prolonged and intensive therapy with the iodides. On rare occasions the disease progresses despite adequate treatment,<sup>10</sup> such examples usually being of the disseminated variety. Continuation of the medication for one month after no further evidence of the disease can be demonstrated is advisable in order to prevent recurrences. It seems worthy of note that

numerous individuals with sporotrichosis have doubtless been stigmatized, in the past, as having syphilis because of a therapeutic response to the iodides.<sup>5</sup> In addition to such medication, judicious roentgen therapy is often useful as a therapeutic adjunct, especially in treatment of the localized lymphangitic type.

#### REPORT OF A CASE OF MULTIPLE DISSEMINATED SUBCUTANEOUS GUMMATOUS SPOROTRICHOSIS

R. F., a white male, aged 70, was admitted to the Dermatology Service of the University of Michigan Hospital on October 9, 1946, because of an extensive cutaneous eruption of several weeks' duration. The patient had first noticed an ery-



FIG. 1. The widespread distribution of lesions is apparent in this photograph.

thematous, split-pea size papule on the lower back which softened and became ulcerated within a few days and was followed rather promptly by lesions which pursued a similar course on the right thigh and right temporal region. Approximately two weeks before admission numerous similar lesions appeared on widely scattered portions of the integument, including the face, neck, trunk and extremities. The only subjective manifestation was mild pruritus.

Before his retirement at the age of 60, the patient had been a lumber dealer and farmer. Within recent years, however, his contact with plants, shrubs and other vegetation had been minimal. During the summer preceding onset of the efflorescence he had eaten fresh vegetables in abundance, but all had been thoroughly cleaned, in-



FIG. 2. Lesions on the left arm shown at close range. Several have ruptured leaving the typical central crater-like depression surrounded by an indurated ring.

sofar as he was aware. Roentgen therapy had been administered to a basal-cell carcinoma of the right cheek with satisfactory result, at the age of 62, and he had had a transurethral resection because of benign prostatic hypertrophy four years later. His past history otherwise was significant only in that he had been told on numerous occasions in the past, because of frequent respiratory infections, that he had chronic bronchitis.

Physical examination at the time of admission was productive of the following: The patient appeared to be in fairly good general health, but had numerous, discrete, apparently indolent, match-head to small cherry-size polymorphous lesions distributed as noted above (figures 1 and 2). Many were firm, erythematous papules while the

central portion of others was soft, fluctuant and contained purulent material. Some of the lesions had ruptured, with spontaneous evacuation of their contents, leaving central crater-like depressions, surrounded by a firm indurated ring, and a few, probably the earliest, had practically healed. The soft tissues about the proximal phalanx of the right great toe and left fourth finger, as well as those of the middle phalanx of the right fourth finger, were erythematous, swollen and tender. There was also evidence of long standing pulmonary emphysema.

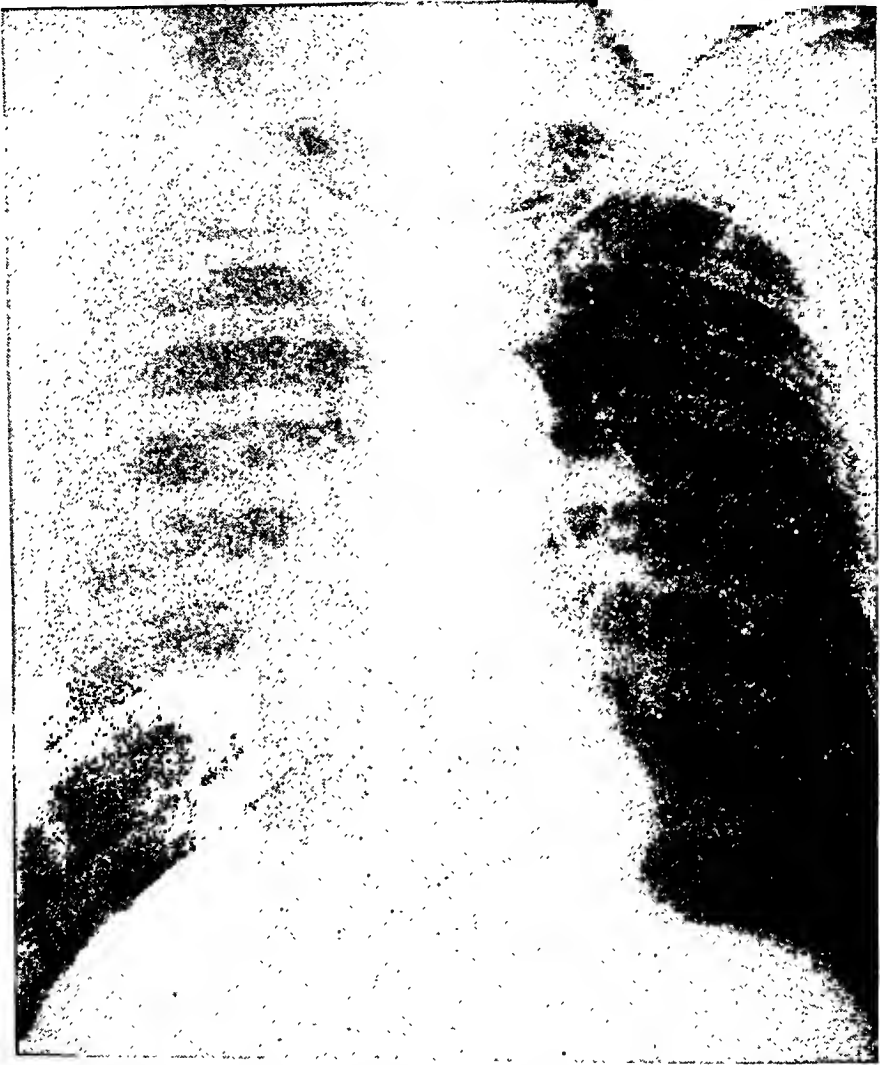


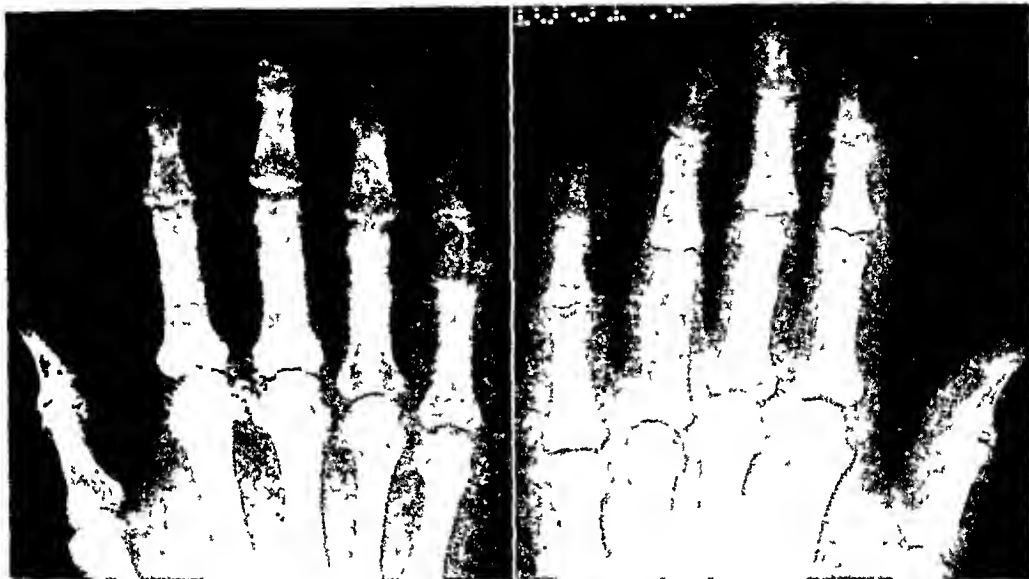
FIG. 3. The triangular shadow of increased density at the inferior border of the right hilum and tenting of the right diaphragm, illustrated here, persisted one year after all lesions of sporotrichosis had involuted being apparently related to atelectasis of the right middle lobe.

Roentgenograms were made of the hands, feet and chest. These demonstrated bilateral pulmonary emphysema of moderately severe degree, a triangular shadow of increased density at the inferior border of the right hilum and tenting of the right diaphragm (figure 3). Exact identity of the latter changes was indeterminate, although atelectasis of the right middle lobe was suspected. Destructive osseous changes involving the phalanges noted above were also apparent (figures 4 and 5). The roentgenologist was of the opinion that osteomyelitis, Boeck's sarcoid and metas-



tatic neoplasm could not be excluded from the realm of diagnostic possibilities as having induced the skeletal changes.

Tissue for microscopic examination was obtained from several lesions in various stages of evolution, and purulent material was aspirated from numerous intact pustules and inoculated on Sabouraud's medium. Pathologically most of the lesions showed a chronic process, with morphological features interpreted as those of mixed tuber-



FIGS. 4 and 5. Destructive changes apparently of sporotrichotic origin, involving the middle phalanx of the right fifth finger and proximal phalanx of the left fourth finger.

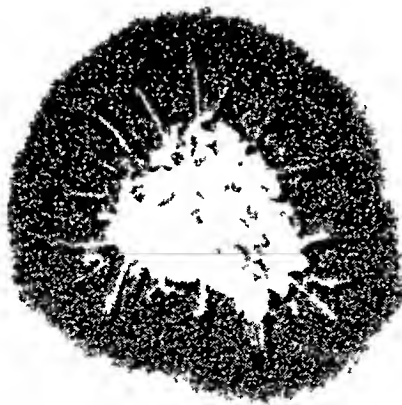


FIG. 6. The original colony of *S. schenckii* as cultured from the case recorded here. Note the convolutions. After three weeks the entire colony became darkly pigmented.

culous and pyogenic granulation tissue. Special stains did not reveal spirochetes, tubercle bacilli or evidence of fungi. All culture tubes and Petri dishes demonstrated the rather prompt growth of a sporotrichum which was identified after further definitive studies<sup>2</sup> as *S. schenckii* (figure 6). Comprehensive laboratory studies, with exceptions as noted above, were consistently negative.

Intensive and protracted therapy utilizing potassium iodide resulted in prompt and permanent involution of the cutaneous eruption. A roentgenogram of the chest approximately one year after his admission to the hospital showed the pulmonary findings to be unchanged, while roentgenograms of the hands and feet revealed that the osseous lesions had healed, leading to the suspicion that these latter were probably of mycotic origin, possibly secondary to deep seated cutaneous lesions in overlying soft tissues.

### SUMMARY

1. Sporotrichosis is a disease to be reckoned with on occasion by physicians in every branch of medicine. *S. schenckii* and *S. beurmanni*, of species within the genus *sporotrichum*, are the usual etiological agents. All species are frequent saprophytes, most often on vegetable material, but also at times on humans and on other animals. The disease probably develops in most instances because of a lessened resistance of the host at the time of inoculation.

2. Manifestations of the disease are polymorphous, this feature often being of diagnostic import especially as regards lesions of the skin. Although sporotrichosis is usually divided, for purposes of description, into the cutaneous and systemic types, it is worthy of note that a preponderance of all cases demonstrates involvement of the integument to a variable degree, and that demonstrable visceral lesions are most unusual. Of all the deep mycoses, sporotrichosis is the only one for which there exists a specific therapeutic agent.

3. An unusual case of multiple, disseminated, subcutaneous, gummatous sporotrichosis, with probable secondary osseous lesions is reported.

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## THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN AND SODIUM PARA-AMINOHIPPURATE BY CONTINUOUS INTRA-VEINUS DRIP \*

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THE use of penicillin with and without heparin in the treatment of subacute bacterial endocarditis has justified the hope for temporary or permanent arrest of this disease. The addition of sodium para-aminohippurate as an enhancing agent may increase the effectiveness of penicillin therapy. Its use with penicillin in the treatment of subacute bacterial endocarditis has been reported by Loewe<sup>1</sup> and others with evident success.

Our patient was thought worthy of report because of: (1) the finding of a relatively resistant organism identified as *Streptococcus viridans*, (2) the large quantities of penicillin and para-aminohippurate administered, and (3) the apparent success of this treatment.

### CASE REPORT

J. W., a 50 year old white male, was admitted to the Bryn Mawr Hospital on June 5, 1946 with a history of fever, muscle aches, anorexia, shoulder pain, weakness, and dyspnea of seven weeks' duration.

On admission his temperature was 100° F., pulse 96, respirations were 22, and blood pressure was 140 mm. Hg systolic and 80 mm. diastolic.

At the age of 17 he had experienced an illness diagnosed as rheumatic fever by his family doctor. He was told that following this attack he was left with "leaky heart valves." Aside from slight dyspnea on exertion he led a normal life. Six years later, at the age of 23 years, he had another attack of rheumatic fever, this time of lesser severity. He was in bed for "only a few days." Fifteen years later, at the age of 38 years, he had still another attack of what was diagnosed as rheumatic fever. He was confined to bed again "for only a few days." During none of these attacks were there any signs or symptoms suggesting decompensation. He states that he was well following this last episode, 12 years before admission, until the present disease became apparent.

Seven weeks before admission to the hospital the patient observed that he felt weak, was losing his appetite, had vague muscle aches, and was more dyspneic than usual on exertion. At the time he was working as a foreman in a machine shop which required him to stand for long periods of time. When these symptoms presented he stopped work and remained in bed for the seven weeks preceding his admission to the hospital. He had evening temperature rises nightly to 102° to 103° F., which returned to normal in the morning. Ten days before admission he complained of neck and bilateral shoulder pain. His only medication at the time was sodium salicylate. Other than as already stated his previous medical history was negative.

On physical examination he was a pale, thin man resting in bed without marked distress. He was found to have an enlarged heart with harsh apical systolic and diastolic murmurs. His spleen and liver were not palpable and no petechiae were found.

His electrocardiogram showed a low T<sub>2</sub>, negative T<sub>3</sub>, and low T CR<sub>5</sub>. A

\* Received for publication July 21, 1947.

urinalysis showed a trace of protein and 50 to 60 red blood cells, which in later urinalyses were not observed. A blood culture taken on the day of his admission proved to be positive, containing *Streptococcus viridans*, which was reported to be "very sensitive to penicillin."

He was started on 500,000 units of penicillin daily by the intramuscular route by his attending physician. However, for some reason, after four days of this treatment the penicillin was stopped following a return of his temperature to normal. A blood culture taken one day later was reported negative and the patient was discharged apparently improved on June 18, 1946.

On arriving home the patient received the following treatment from his attending physician. Bi-weekly for three weeks he received 300,000 units of penicillin in beeswax for a total of 1,800,000 units of penicillin. He was then placed on oral penicillin with a daily dose of 300,000 units. This dosage was maintained for 73 days with a total of 21,900,000 units. As the patient again developed evening temperature rises despite this treatment he was again placed on sodium salicylate (60 gr. per week). The oral penicillin was discontinued. The sodium salicylate was administered for one week and as there was no response, the patient was again admitted to the Bryn Mawr Hospital on September 27, 1946, this time under ward care.

On readmission his temperature was 101° F., pulse 102, respirations were 22, and his blood pressure was 130 mm. Hg systolic and 70 mm. diastolic. His complaints at this time were fever, anorexia, weakness, and right shoulder pain which he attributed to the fact that he slept on his right side all the time, because sleeping on his left side made him "heart conscious."

On physical examination he appeared pale, thin, and anxious. His heart was enlarged and there were harsh apical systolic and diastolic murmurs. There were infrequent extrasystoles. The spleen and liver were not palpably enlarged, the upper border of liver dullness being at the fourth right intercostal space in the midclavicular line. No petechiae were found.

Positive blood cultures were obtained on the fifth, the eleventh, and the thirteenth days, each time demonstrating *Streptococcus viridans*. The sensitivity of the organism was tested, and it was found to be sensitive at the level of 0.5 unit per c.c. Penicillin was started by this time at a dosage of 1,000,000 units per day in saline. It was given mostly by the interrupted intramuscular route, but on three days the intravenous route was used in a solution of 1,000 c.c. 5 per cent glucose in normal saline solution. His temperature dropped to normal, and all treatment was stopped after 11 days.

Blood cultures were taken regularly and nine days after the cessation of penicillin treatment another positive blood culture was obtained and the organism identified as *Streptococcus viridans*. While waiting to obtain a supply of para-aminohippurate he was again placed on 1,000,000 units of penicillin daily by the interrupted intramuscular route to save his veins preparatory to continuous intravenous treatment.

Realizing the possible hazard of intravenous therapy in a cardiac patient, the following studies were performed. Phenolsulfonphthalein dye excretion test was 40 per cent. Urea clearance test showed 86 per cent normal. The plasma protein was 7.5 with 4.6 albumin and 2.5 globulin. The blood urea nitrogen was 11 mg. per cent. The prothrombin time was 90 per cent. The blood volume was estimated by the T-1824 (Evans Blue Dye) method and found to be 5,330 c.c. The expected blood volume for this patient was 5,370 c.c. The plasma volume was 3,518 c.c., and the cell volume was 1,812 c.c.

By this time the sodium para-aminohippurate\* had been obtained and intensive intravenous treatment was initiated. During the treatment daily plasma samples were

\* The authors wish to express their gratitude to Sharpe and Dohme, Inc., for the supply of sodium para-aminohippurate and their aid in performing the estimations of plasma penicillin levels.

taken each morning at the same time. This time coincided with the change of intravenous solutions.

In view of the resistance of the organism estimated at 0.5 unit per c.c., the approximate penicillin level needed in this case for the bactericidal effect was estimated according to the work of Loewe.<sup>2</sup> In his work he found serum assays of 0.1 unit per c.c. to be obtained by administering 100,000 units of penicillin per day by the continuous intravenous drip method. This would have made our optimum dosage 500,000 units, but as we had already learned that 1,000,000 units per day were insufficient to inhibit or kill the organism, we chose an arbitrary dose of 5,000,000 units per day.

Loewe<sup>3</sup> also found in his work on para-aminohippurate that when levels of PAH were over 10 mg. per cent he could obtain increases of penicillin levels three to six times that of the control. He estimated that to obtain PAH levels of 30 to 40 mg. per cent it was necessary to administer PAH at the rate of 150 mg. kg./hour. This would mean for our patient weighing 150 pounds that 245 grams in 24 hours would be necessary to gain 30 to 40 mg. per cent blood level of PAH. As our supply was limited and we wished to prolong the treatment as long as possible, we decided upon 200 grams as our daily dosage.

The plan of treatment was as follows:

For the first three days the continuous intravenous drip included daily:

- (1) 5,000,000 units of penicillin
- (2) 2,000 c.c. 5 per cent glucose in distilled water
- (3) 50 mg. heparin (this was included merely to facilitate the mechanics of keeping a continuous intravenous drip running without clotting at the needle, and was not administered for any therapeutic value)

On the fourth day the solution was changed to include:

- (1) 5,000,000 units of penicillin
- (2) 2,000 c.c. 5 per cent glucose in distilled water
- (3) 50 mg. heparin
- (4) 200 grams of sodium para-aminohippurate

This was continued for 10 days.

The total quantity of penicillin over the 13 day period was 65 million units.

On the first day of PAH administration the patient experienced two involuntary bowel movements and complained of crampy abdominal pain of moderate severity. However, these reactions were not experienced after the first day of PAH administration. It was found that if the drip was sped up to the rate of 30 drops per minute or more, the crampy abdominal pains could be reproduced and as soon as the rate was returned to the desired rate of 20 to 22 drops per minute this pain was eliminated.

In addition to the 2,000 c.c. of fluid given in the intravenous drip daily, the patient was kept on a full house diet and allowed 1,000 c.c. of additional fluid by mouth. He was given maintenance doses of digitalis.

Following this treatment (figure 1) the patient was subjected to repeated blood cultures, all of which proved sterile. (The blood culture medium was infusion broth with added glucose, para-aminobenzoic acid, and penicillinase.) The urea clearance test was found to be 40 per cent normal. This was rechecked two months later and found to be 60 per cent normal. His temperature was constantly normal. His sedimentation rate, which had been a vertical curve before treatment, was starting to flatten out to a diagonal curve with a reading of 25 mm. in 60 minutes. He was fully compensated as to his cardiac state. His sole complaint was of right shoulder pain which has since responded to physiotherapeutic measures.

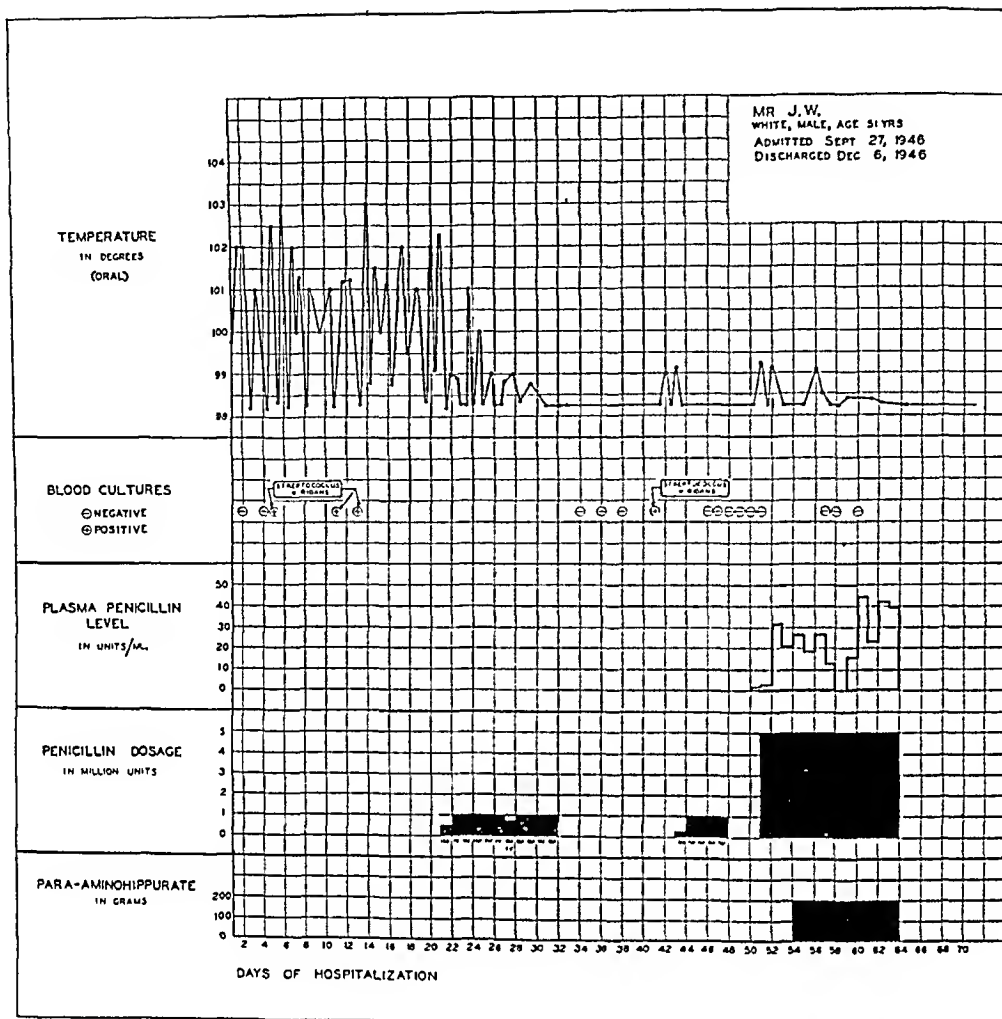


FIG. 1.

He was discharged eight days later. He was followed as an out-patient and seen every two weeks. At each visit he had a blood culture taken, all of which were negative. He was afebrile for six months. His sedimentation rate six months after discharge was a horizontal line reading 7 mm. in 60 minutes. He returned to work in a machine shop with no apparent difficulty in maintaining a full eight hour work day.

### DISCUSSION

To administer 2,000 c.c. of solution by intravenous drip over 24 hours it was found that the rate had to be maintained at 20 to 22 drops per minute, and this quite naturally entailed constant supervision of the patient. It is also to be observed that this patient was unusually coöperative and bore the tedium of the 13 days of constant drip with remarkable patience. At times the position of the needle in the vein was not changed for 60 hours with no mechanical obstruction to the continuous flow of the solution.

Plasma penicillin levels taken daily on this patient were assayed by the Florey technic and did, when averaged for each period of treatment, show a definite

increase following the administration of PAH in conjunction with penicillin over the administration of penicillin alone.

On the eighth day of treatment the penicillin assay showed no penicillin present. Although this may be a laboratory error, it can surely not be dismissed as such. No explanation could be found for this.

Using the theoretical level of penicillin<sup>2</sup> calculated on 0.1 unit per ml. per daily dose of 100,000 units it will be found that practically all plasma penicillin levels were well over the theoretic level (table 1). The administration of 5,000,000 units of penicillin per day should yield, by theory, a level of 5.0 units per ml.

TABLE I  
Plasma Penicillin Levels in Units/ml.

Day	Theoretical	Actual	Deviation
1	5.0	2.3	-2.7
2	5.0	31.6	26.6
3	5.0	20.8	15.8
			Total -2.7 +42.4
4	5.0	27.0	22.0
5	5.0	18.2	13.2
6	5.0	27.0	22.0
7	5.0	13.6	8.6
8	5.0	0.0	-5.0
9	5.0	16.1	11.1
10	5.0	43.6	38.6
11	5.0	22.3	17.3
12	5.0	41.2	36.2
13	5.0	39.2	34.2
			Total -5.0 +203.2

Granting that the use of PAH results in a higher penicillin blood level than when the same dose of penicillin is given alone, the authors question whether the difficulties and expense attendant upon prolonged intravenous administration of PAH are justified when the same high blood penicillin levels might be obtained by the use of larger penicillin dosages.

In reporting this case the authors realize full well that definite conclusions in evaluating the efficacy of any therapeutic regime cannot be drawn from one case report and so submit this case report to add to other cases similarly treated for overall evaluation in the future.

#### CONCLUSIONS

a. A case of subacute bacterial endocarditis due to *Streptococcus viridans* is presented.

b. Two previous attempts at penicillin treatment were unsuccessful in arresting the disease process.

c. The administration intravenously daily for 13 days of a solution containing 5,000,000 units of penicillin, plus 200 grams of sodium para-aminohippurate for the last 10 days of this treatment, is recorded as the treatment used. Heparin in small doses was added to facilitate the continuance of the constant venoclysis.

d. Plasma penicillin levels showed a definite increase over the expected estimated levels. On the average they were greater with the administration of sodium para-aminohippurate concurrently. However, the authors feel this same elevation could be effected more easily by merely increasing the penicillin dosage.

e. A follow-up of six months on this patient found him well and able to earn his living at his former occupation.

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## EDITORIAL

### GRADUATE EDUCATION IN ALLERGY

IN a recent survey of hospital and medical college residencies and fellowships in allergy conducted by the Subcommittee on Graduate Education of the American Academy of Allergy it was found that 17 institutions in the United States offer facilities for this type of training. Of this group eight stated that it was difficult to attract high grade men. A consideration of this problem furnishes the basis of this report.

There would seem to be several reasons for this situation. Ignorance of the opportunities available for research and clinical training in allergy is one. Failure of the present facilities to attract is another. It is also probable that our courses in medical schools under-emphasize the importance of allergic diseases,<sup>1</sup> and as Barr<sup>2</sup> says, "it is more than deplorable that many young internists have been permitted to finish their training without contact

GRADUATE EDUCATION IN ALLERGY (FELLOWSHIPS AND RESIDENCIES)

	Council Approved	Number	Filled	Total Trained
1. Brooklyn Jewish Hospital	yes	3	2	10
2. Duke University Hospital	—	1	1	—
3. Johns Hopkins Hospital	yes	1	1	11
4. Mass. General Hospital (Harvard)	yes	1	0	9
5. Michigan University Hospital	—	3	3	12
6. Milwaukee County Hospital (Marquette)	yes	1	1	—
7. Montefiore Hospital (Pittsburgh)	yes	1	1	3
8. New York Hospital (Cornell)	—	1	1	2
9. Northwestern University	yes	2	1	2
10. Roosevelt Hospital	yes	2	2	7
11. University Hospital (N. Y. University)	yes	2	2	6
12. University of Illinois	yes	4	2	2
13. University of Pennsylvania Hospital	—	1	1	—
14. University of Virginia Hospital	yes	3	3	9
15. Veterans Hospital (Aspinwall, Pa.)	yes	2	2	2
16. Virginia Medical College	yes	2	2	2
17. Washington University (Barnes Hospital)	—	1	0	1
	12	31	25	78

with allergy and allergic thought." This is particularly true since few hospitals rotate their internes and assistant residents through the allergy clinic. The result has been that our best internes and residents, casting about for a field in which to do special study, have not had enough contact with the allergic diseases to be interested in them.

<sup>1</sup> SWINEFORD, OSCAR, JR.: Undergraduate education in allergy, Jr. Assoc. Am. Med. Coll., 1946, xxi, 265-270.

<sup>2</sup> BARR, D. P.: The relationships of allergy to medicine, Jr. Allergy, 1945, xvi, 61.

The table indicates the 17 hospitals and medical schools where fellowships and residencies in allergy are available. Of these, 12 have been approved by the Council on Medical Education and Hospitals of the A.M.A. and of the balance, four have applications in process. Twenty-five out of 31 openings are filled and the physicians trained through these facilities now number seventy-eight. The term in most instances is one year, generally renewable for one or two more years and the monthly stipend ranges from \$50 to \$280. In all cases there is close contact with the departments of Medicine or of Pediatrics and with the departments of Oto-Rhinology and of Dermatology. Opportunities for research are available and the resident is encouraged to interest himself in the basic sciences of Immunology and Bacteriology.

The individual pattern of the allergy services varies considerably. At the Brooklyn Jewish Hospital and at the Milwaukee County Hospital (Marquette) the residents live in the hospital, have the duties and responsibilities usually associated with a house officer, provide consultations on other services and attend the allergy clinic. At the University of Michigan Hospital, the residents in allergy are selected from the assistant resident and resident staff after three years of training in internal medicine or pediatrics. They serve as residents in allergy for two years, having the supervisory duties of a house officer and engaging in research and in undergraduate teaching. They have close contact with the general medical staff, the department of infectious diseases and the various specialty departments. At the University Hospital, New York (formerly the N. Y. Post-Graduate Hospital), the resident in allergy has charge of all allergy cases admitted from the adult allergy clinic and engages in research, the activities of the Allergy Clinic and related departments, and is also assigned to the department of Immunology and Bacteriology for additional work. He is required to continue his contact with internal medicine by attending medical out-patient clinics and conferences. The same program is in most respects followed by the Montefiore Hospital (University of Pittsburgh), University of Virginia Medical College Hospital, the Veterans Hospital (Aspinwall) and Virginia Medical College.

In a number of institutions the work is more characteristic of a research fellow with added training in clinical medicine, the specialties related to allergy and the fundamental departments of Immunology and Bacteriology. In these institutions there is less clinical responsibility on the in-patient services, the emphasis being placed upon research. Barnes Hospital (Washington University), Duke University Hospital, Johns Hopkins Hospital, Massachusetts General Hospital (Harvard), New York Hospital (Cornell), Northwestern University Medical College, Roosevelt Hospital (New York), University of Illinois, and University of Pennsylvania Hospital, follow this pattern. Some of these institutions offer post-graduate education and in this group the University of Illinois and the University Hospital of New York University are examples.

In spite of these well integrated and well planned programs, the oppor-

tunities are not attracting many high grade men. The development of graduate education in allergy is only a small part of the problem of graduate education in general. The relative absence of organization of the graduate educational facilities in our hospitals and medical schools, as compared with the courses developed for undergraduate and post-graduate education, is recognized by the Commission on Graduate Education.<sup>3</sup> Undergraduate medical education and post-graduate courses are largely supported by student fees and university endowments, whereas education at the resident and fellowship level is for the most part dependent upon grants for special projects. Most hospitals have trouble enough to meet their necessary expenses without appropriating additional funds for what primarily amounts to an educational program. The donors of funds have placed too much emphasis on research in the laboratory and too little, especially in the field of allergy, on the development of young men whose training is primarily clinical. It is rather paradoxical to see large endowments of medical schools devoted to the training of future physicians carefully selected for outstanding qualities of leadership and then, having provided such a preëminent educational experience, fail to establish opportunities for hospital or fellowship training in which these qualities for leadership can be activated for outstanding service.

It is important to discourage undue specialization, but it is also true, especially in internal medicine, that no physician can know completely the ramifications of its important subdivisions notably allergy, infectious diseases, psychosomatic medicine, cardiology, peripheral vascular disease, hematology, metabolism, endocrinology and the special diseases of the lungs and gastrointestinal tract. Instead of leaving to chance the selection by residents and fellows of one of these smaller divisions, would it not be the part of wisdom and foresight for the leading medical institutions to group these various specialties and organize them for graduate education? Allergy would fit well into a group comprising also infectious diseases, immunology and psychosomatic medicine. Similar associations comprising cardiology, peripheral vascular disease and hematology, or metabolism and endocrinology, are desirable and are necessary if young men are to be trained in strategic centers for leadership in teaching, research and consultation practice.

In the future development of allergy, emphasis will be placed on the widening scope of hypersensitivity in disease, not only to include the common allergic ailments but also the wide variety of tissue changes due to sensitization as exemplified by the researches of Landsteiner, Rich, Klemperer and others. The young man choosing allergy as a subspecialty will consider himself a part of the whole field of applied immunology. Yet, fundamentally, as Cooke<sup>4</sup> points out, "Education in allergy must be based upon

<sup>3</sup> Graduate Medical Education, Report of the Commission on Graduate Education, 1940, Univ. of Chicago Press, page 14.

<sup>4</sup> COOKE, R. A.: Allergy in relation to medical education, *Clinics*, 1946, v, 322.

and follow a thorough training in the broad field of internal medicine or pediatrics." To divert the resident or fellow into allergy without such preliminary training will defeat the prime purpose of graduate education in allergy, which is to furnish for teaching, research and practice, men who will not only be familiar with the concepts of hypersensitivity and immunology but will also understand their clinical application.

HORACE S. BALDWIN, M.D.,  
Chairman of Sub-committee on Graduate  
Education, American Academy of Allergy,  
and

W. C. SPAIN, M.D., F.A.C.P.,  
Chairman of Committee on Education,  
American Academy of Allergy

## REVIEWS

*Textbook of the Rheumatic Diseases.* Edited by W. S. C. COPEMAN, O.B.E., M.D., F.R.C.P. 612 pages; 17 × 24.5 cm. The Williams and Wilkins Co., Baltimore 2, Md. 1948. Price, \$12.50.

Dr. Copeman has given his volume the title, "Textbook of Rheumatic Diseases." In so doing he has stated a purpose which the text has fulfilled admirably. The book expresses the British point of view, particularly in that the author gives "non-articular rheumatism" more prominence than do American students of the subject. Perhaps English experience warrants this, but fibrositis is not so frequent in its occurrence as a recognizable entity in this country. On the other hand with the rise of psychosomatic medicine, psychogenic rheumatism occupies a much more prominent place in America than this English volume allots to it. However, the correctness of either view is not yet established.

The arrangement of the textbook in devoting so much discussion to the anatomy and what is known concerning the physiology of joints, as well as the relation of other tissues to rheumatic diseases, affords an introduction and background to the field which is most desirable and often is lacking. This not only prepares one for the clinical manifestations of joint disease but guides one naturally to the discussions of the pathology of joint disease, which is presented in a coördinated fashion. The chapters on pathology are to be particularly commended to the reader. They present this sparse field, in which information, either ante-mortem or post-mortem is so difficult to obtain, in a manner which suggests the interrelationship of the various forms of inflammatory joint disease but hardly emphasizes this relationship sufficiently. Likewise in the clinical chapters on inflammatory joint disease this possible, if not probable, close linkage could be more extensively dwelt upon. Perhaps the collective authorship, which gives much that is to be desired in that each phase is dealt with by one of large experience in the particular subject at hand, is in a measure responsible for this. So often with this arrangement coördinated relationship fails to develop, which seems to be the case here. Many times the treatise suffers when handled in this manner. For instance, disseminated lupus erythematosus is mentioned in a short section under the heading, "Other Pathological Conditions Simulating Arthritis," and by another author in discussing "Serological Reactions with Haemolytic Streptococci" mention is made that—"Results with non-rheumatic controls were weak or doubtful except in psoriasis and lupus erythematosus." Whereas the relationship of rheumatoid arthritis or Still's disease, or for that matter, even rheumatic fever to disseminated lupus, is by no means established, much less understood, it is nevertheless too strongly suggested both clinically and pathologically to be passed over so lightly.

In dealing with the affections of the shoulder joint, the author has attempted to bring about some clarification of the maze of conditions which are so freely brought together under the heading of "Brachial Neuralgia." Any effort toward this end is laudable and he not only has seen the need for this, but has gone a long way toward more accurate diagnosis. Likewise with the sciatic nerve, he resists the tendency of the day to attribute most, if not all, sciatic pain to the protrusion of a ruptured intervertebral disc, and accords to other affections of this area their proper place. This effort to combat looseness in diagnosis is sorely needed, for rheumatic diseases in general suffer from this lack of accurate differentiation.

The chapter dealing with "The Radiology of the Rheumatic Diseases" again strives for clarity and the emphasis given to early bone and joint changes is of particular value. We are prone to consider the radiological diagnosis of gout as readily made if any changes are present, but the author has realized the confusion that may

arise both in the differentiation from the changes of rheumatoid arthritis and more particularly those instances of atypical rheumatoid arthritis where either a non-arthritis or recurring brief and sharply defined attacks lead to clinical difficulties. He is quite aware of the tendency to consider early changes as lacking or unrecognizable and appreciates the desirability of early detection of rheumatoid arthritis as such, when a cessation of activity would leave a joint at least functionally intact. These early changes are pointed out and in an unusually well illustrated chapter much is contributed to this early diagnosis, so much to be desired.

The section concerned with physical therapy and the orthopedic problems of rheumatic diseases is excellent. Here the author stresses the importance of the prevention of deformity which the patient is willing to dispense with because it is painful and the doctor is so prone to overlook. Likewise the indications and contraindications are made clear, as well as what may be expected of the various types of physical therapy. This is an important contribution. The function of the orthopedic surgeon in the prevention of deformity is properly stressed, which adds much to a coördinated approach to rheumatic diseases and broadens the appreciation of the problem. In rheumatoid arthritis, for example, this more comprehensive approach makes both doctor and patient aware of the fact that it is the results of the disease which impose the crippling deformities, that the joint has no working margin and when a joint is inflamed by so much is its function limited.

The arrangement of the volume is good, the index is well arranged and makes the information contained in the text readily accessible, and the illustrations are extremely well done and add much to the clarity of the text. The author is to be congratulated upon his efforts and, except for the somewhat disconnected approach to the problem of inflammatory joint disease of unknown etiology, has made a valuable contribution. Here, again, this may be only a matter of point of view.

CHARLES W. WAINWRIGHT

*Bone Marrow Biopsy: Haematology in the Light of Sternal Puncture.* By S. J. LEITNER, M.D. English Translation Revised and Edited by C. J. C. BRITTON, M.D., Ch.B., D.P.H., and E. NEUMARK, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P. 433 pages with 7 plates (6 in color) and 194 text-figures. 24.5 × 16 cm. Grune & Stratton, New York. 1949. Price, \$8.50.

This work is an English translation of the recent second Swiss edition of Leitner's monograph. It is based on investigations carried out at the medical clinic of the University of Berne and the first edition was published in the *Folia Haematologica* in 1941. The wider use of sternal puncture in clinical study has in recent years brought forth much that is new and, in some instances, has changed the entire hematological aspect of certain diseases. In his second edition Leitner has succeeded in a complete modernization of his material, keeping well apace with all that is new and worthwhile in hematology.

The rather urgent need for a really comprehensive work on the bone-marrow has been recognized by all hematologists, clinicians and pathologists. It is interesting that the translator, Britton, discloses that he himself was working on such a volume when asked to review and edit this work. It is still true today that, at least in certain fields of hematology, the Continental and Anglo-American schools of thought vary rather widely. Hence, it is fortunate that Britton was given wide discretion by the author in editing, alteration and the incorporation of new material. The net result is pleasing to the American reader who seldom is disturbed by the "foreign" flavor he is ingesting.

Despite the very specialized nature of this study the author well realizes the impossibility of divorcing bone-marrow biopsy from the history, examination and

other laboratory findings in any given hematological case. Accordingly, in the description of the blood dyscrasias, adequate clinical data are incorporated when pertinent. In fact, 81 illustrative case histories are included. The author's cell terminology throughout the treatise cannot be criticized if for no other reason than that, for a long time, blood cell terminology has been in complete chaos. Some hope for the future is offered in that, at this writing, active efforts in America are being taken to try to secure a single accepted terminology.

The quality of the illustrations in this volume is adequate. As to number, the reader of a work of this type is hungry for illustrations and the inclusion of even double the quantity would not have surfeited the earnest student.

Despite minor short-comings, such as the inclusion of English but utter omission of American workers who first revealed the clinical implications of the Rh factor, the work is sound and reliable. Not particularly because of the paucity of monographs on this subject but because of its intrinsic worth, this book should be acquired by the practicing hematologist to add to his comfort in his daily stint with problems of the bone marrow.

H. R. P.

*Practical Aspects of Thyroid Disease.* By GEORGE CRILE, JR., M.D., F.A.C.S., Department of Surgery, Cleveland Clinic. 355 pages, 20.5 × 14 cm. W. B. Saunders Co., Philadelphia. 1949. Price, \$6.00.

The author's stated purpose is to present diseases of the thyroid in such a way that the physician may gain a better understanding of the aims of the surgeon, and that the surgeon may better appreciate what the internist and radiologist can accomplish. This purpose is admirably achieved. Dr. Crile strikes a nice balance between medical and surgical opinion and between new and conservative measures, in a way which gives the reader great confidence in the author's judgment.

The whole field of thyroid disease is covered. The diagnosis of hyperthyroidism and its treatment with iodine, antithyroid drugs, roentgenotherapy and radioactive iodine, are well and fully discussed. Its treatment by thyroidectomy is handled in detail with full description and discussion of preoperative management, anesthesia, technic of operation, postoperative care, complications and results. The author emphasizes the advantages of extracapsular ligation of the inferior thyroid artery. Eighty pages are devoted to malignant diseases of the thyroid, while further chapters deal with endemic goiter, intrathoracic goiter, recurrent hyperthyroidism, congenital abnormalities of the thyroid, and thyroiditis.

This book can be recommended to physician, surgeon, and student. It lives up to its title in being essentially practical with theorizing reduced to a minimum. The format is excellent, and the text well written and easily read. One minor criticism concerns punctuation. Many four, five, or even six line sentences, piling up their clauses, are allowed to ride on to their conclusion without a comma. Small though this complaint is, comfort-stops, at proper intervals, make a great difference to the reader's journey.

H. J. L. M.

*Food Poisoning.* Revised Edition. By G. M. DACK, Ph.D., M.D., Professor of Bacteriology and Director, Food Research Institute, University of Chicago. 184 pages; 15.5 × 23.5 cm. The University of Chicago Press, Chicago 37, Ill. 1949. Price, \$3.75.

This is an excellent review of the epidemiology, symptomatology, cause, and prevention of the common types of gastro-enteritis. It is much more than a mere

enumeration of the poisons and toxins which man can ingest with his food. Each type is discussed in full with illustrative histories. One fascinating record of poisoning is that of a man who, while gorging on mussels which he had just caught, negligently gave a few to a dog which shortly thereafter vomited; to a cat which developed paralysis the next day, and to two kittens which died. The patient himself developed only some nausea and a general numbness around his lips.

Here, too, is an adequate coverage of poisonous plants such as trematol or milk sickness which produces "trembles" in cattle and may produce death in man despite pasteurization which does not destroy the toxin.

Staphylococcal food poisoning is well demonstrated to be due to an enterotoxin elaborated by certain strains of staphylococci with a sudden onset and rapid severe prostration. In contrast, the essentially infectious nature of salmonella outbreaks is substantiated. These two types are well and adequately covered.

A final chapter on causes of gastro-enteritis other than those ordinarily thought of as food poisoning is particularly helpful and is up to date in its summary of bacterial and viral causes.

This book will be useful to every physician.

F. B. B.

*Encyclopedia of Medical Sources.* By EMERSON CROSBY KELLY, M.D., F.A.C.S  
476 pages; 16 × 23.5 cm. The Williams and Wilkins Company, Baltimore. 1948  
Price, \$7.50.

As Editor of "Medical Classics," the author is eminently qualified for the task of preparing such a volume as this encyclopedia of medical sources. While some modern teachers frown upon the association of proper names with signs, operations, syndromes, etc., the historical value of such association is unquestioned. In addition, since medical literature still contains references to proper names, this volume is of real importance.

The author has produced an admirably useful cross-reference volume of medical sources. A list of the authors' names in bold-face type, together with the title and complete reference to their earliest or best work, comprises the main section, and an index lists the medical terms. It is stated in the preface that about 95 per cent of the papers listed have been consulted in the original. Following each author's name there is a notation of his nationality, his field of work, and his year of birth and death; then the syndrome, reaction, test, operation or other contribution is listed, together with the complete title and reference of the article or articles.

Although such a volume cannot be absolutely complete, the author is to be warmly congratulated upon his compilation. He has performed a great service to the medical and allied professions. Physicians, students, research workers, medical historians, and librarians will find this encyclopedia most helpful.

J. E. S.

### BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*An Atlas of Bone-Marrow Pathology.* By M. C. G. ISRAELS, M.Sc., M.D., M.R.C.P.,  
Lecturer and Deputy Director, Department of Hematology, The University and  
Royal Infirmary, Manchester, etc. 79 pages; 25 × 19 cm. 1948. Grune &  
Stratton, Inc., New York. Price, \$6.50.



*Atlas of Oral and Facial Lesions, and Color Film Library.* By RALPH HOWARD BRODSKY, D.M.D., Consulting Oral Surgeon, Department of Hospitals, New York City, etc. With a Foreword by LEROY M. S. MINER, M.D., D.M.D., Formerly Dean, Harvard University Dental School. 127 pages, with slide case containing 100 colored slides; 26 × 17.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$80.00.

*Cardiac Catheterization in Congenital Heart Disease: A Clinical and Physiological Study in Infants and Children.* By ANDRÉ COURNAND, M.D., Associate Professor, Department of Medicine, College of Physicians and Surgeons, Columbia University; JANET S. BALDWIN, M.D., Assistant Professor, Department of Pediatrics, New York University College of Medicine, and AARON HIMMELSTEIN, M.D., Instructor, Department of Surgery, College of Physicians and Surgeons, Columbia University. 108 pages; 28.5 × 20.5 cm. 1949. The Commonwealth Fund, New York. Price, \$4.00.

*Coronary Artery Disease.* By ERNST P. BOAS, M.D., Associate Physician, Mount Sinai Hospital, New York City, and NORMAN F. BOAS, M.D. 399 pages; 21 × 14.5 cm. 1949. Year Book Publishers, Inc., Chicago. Price, \$6.00.

*Diagnosis of Viral and Rickettsial Infections: Symposium Held at the New York Academy of Medicine January 29 and January 30, 1948.* Edited by FRANK L. HORSFALL, JR. 153 pages; 23.5 × 15.5 cm. 1949. Columbia University Press, New York. Price, \$3.75.

*Diseases of the Liver, Gallbladder and Bile Ducts.* 2nd edition, revised. By S. S. LICHTMAN, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Cornell University Medical College, etc. 1135 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, \$18.00.

*Das Elektrokardiogramm: Ein Handbuch für Theorie und Praxis.* By DR. EUGEN LEPESCHKIN, Balneologisches Institut, Bad Nauheim. 336 pages; 24 × 16 cm. (paper-bound). 1947. Verlag Von Theodor Steinkopff, Dresden and Leipzig.

*The Epidemiology of Hemolytic Streptococcus During World War II in the United States Navy.* By ALVIN F. COBURN, M.D., The Rheumatic Fever Research Institute, Northwestern University Medical School, and DONALD C. YOUNG, M.D., Medical Director, Communicable Disease Service, Herman Kiefer Hospital. 229 pages; 23.5 × 15.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$4.00.

*Evaluation of Chemotherapeutic Agents: Symposium Held at the New York Academy of Medicine, March 25 and 26, 1948.* Edited by COLIN M. MACLEOD. 205 pages; 23.5 × 15.5 cm. 1949. Columbia University Press, New York. Price, \$4.00.

*Food Poisoning.* Revised Edition. G. M. DACK, Ph.D., M.D., Professor of Bacteriology and Director, Food Research Institute, The University of Chicago. 184 pages; 23.5 × 15.5 cm. 1949. The University of Chicago Press, Chicago. Price, \$3.75.

*The Fundamentals of Pulmonary Tuberculosis and Its Complications for the Student, the Teacher, and the Practicing Physician.* Sponsored by the AMERICAN COLLEGE OF CHEST PHYSICIANS. Editor: EDWARD W. HAYES, M.D. Editorial Committee: ANDREW L. BANYAI, M.D., HERMAN HILLEBOE, M.D., J. ARTHUR MYERS, M.D., and J. WINTHROP PEABODY, M.D. 480 pages; 24 × 16 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$9.50.

*The Invert and His Social Adjustment.* 2nd ed. By ANOMALY, to which is added a Sequel by the same author; with an Introduction by R. H. THOULESS, M.A., Ph.D. 290 pages; 17.5 × 10.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, \$3.00.

*Kayne, Pagel, and O'Shaughnessy's Pulmonary Tuberculosis: Pathology, Diagnosis, Management and Prevention.* 2nd Edition. Revised and partly rewritten by WALTER PAGEL, M.D., Pathologist, Central Middlesex County Hospital, London; F. A. H. SIMMONDS, M.A., M.D., D.P.H., Medical Director, Clare Hall County Hospital, Middlesex; N. MACDONALD, M.B., M.R.C.P.Ed., Physician to the Chest Clinic, Redhill County Hospital, Middlesex, and L. FATTI, F.R.C.S., Thoracic Surgeon, Hillingdon County Hospital and Harefield County Hospital, Middlesex. 720 pages; 25 × 17.5 cm. 1949. Oxford University Press, New York. Price, \$18.50.

*Medical X-ray Protection Up to Two Million Volts.* Handbook 41. Written by a sub-committee of the National Committee on Radiation Protection. 43 pages; 20 × 13 cm. (paper-bound). 1949. National Bureau of Standards, U. S. Department of Commerce, Washington, D. C. Price, 15 cents.

*Observations on the Pathology of Hydrocephalus. Medical Research Council Special Report Series No. 265.* By DOROTHY S. RUSSELL. 138 pages; 24.5 × 15 cm. (paper-bound). 1949. His Majesty's Stationery Office, London. Price, Six shillings, net.

*Operative Surgery.* By FREDERICK C. HILL, B.A., M.S. (Surg.), M.D., Associate Professor of Surgery, The Creighton University School of Medicine, Omaha; Foreword by CHARLES W. MAYO, B.A., M.S. (Surg.), M.D., Section on Surgery, Mayo Clinic, Rochester. 698 pages; 24.5 × 16 cm. 1949. Oxford University Press, New York. Price, \$12.75.

*Die Permeabilitätspathologie Als Die Lehre Vom Krankheitsbeginn.* By PROF. DR. HANS EPPINGER. 755 pages; 25.5 × 18 cm. (paper-bound). 1949. Springer-Verlag, Vienna. Price, Sch. 28.50; bound, Sch. 29.40.

*A Primer of Electrocardiography—2nd edition, revised.* By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, etc., and TRAVIS WINSOR, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California Medical School, etc. 245 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, \$4.50.

*Some Common Psychosomatic Manifestations.* By J. BARRIE MURRAY, M.A., M.D. (CANTAB.), M.R.C.P., Diagnostic Physician, Tavistock Clinic, etc. 101 pages; 18.5 × 12.5 cm. (paper-bound). 1949. Oxford University Press, New York. Price, \$2.50.

*The Uses of Penicillin and Streptomycin—Porter Lectures, Series 15.* By CHESTER SCOTT KEEFER, M.D., Wade Professor of Medicine, Boston University School of Medicine, etc. 72 pages; 22 × 14 cm. 1949. University of Kansas Press, Lawrence, Kansas. Price, \$2.00.

*Veterans Administration Technical Bulletins—Series 10, Volume II, 1948.* 183 pages; 27 × 20.5 cm. January, 1949. Veterans Administration, Washington. Price, Not for sale—limited edition for distribution to VA hospitals and medical libraries.



WILLIAM S. MIDDLETON, M.D., Sc.D., F.A.C.P., Madison, Wis.,  
President-Elect, The American College of Physicians

(See following page for biography)

## COLLEGE NEWS NOTES

WILLIAM SHAINLINE MIDDLETON, M.D., Sc.D., F.A.C.P., MADISON, WIS.,  
PRESIDENT-ELECT, THE AMERICAN COLLEGE OF PHYSICIANS

Born, Norristown, Pa., January 7, 1890; M.D., 1911, University of Pennsylvania School of Medicine; Instructor in Medicine, 1912-1915, Assistant Professor of Medicine, 1915-1923, Associate Professor of Medicine, 1923-1933, Professor of Medicine, 1933 to date, and Dean, 1935 to date, University of Wisconsin Medical School; Physician, State of Wisconsin General Hospital since 1935; Diplomate and for many years Secretary-Treasurer, American Board of Internal Medicine; Fellow of the American College of Physicians since 1929.

Dr. Middleton has had an illustrious career, characterized by outstanding service to medical education, medical science and the Medical Corps of the U. S. Army. He is the author of a great host of published articles appearing in leading journals over the country. During World War II, with the rank of Colonel, he served with great distinction as the Chief Consultant in Medicine in the European Theater of Operations of the U. S. Army.

Besides being a member of his county and state medical societies, he is a Fellow of the American Medical Association, a member of the Association for Clinical Investigation, Central Society for Clinical Research, an honorary foreign member of the Association of Physicians of Great Britain and Ireland, a Fellow of the Royal College of Physicians of London, an honorary Fellow of the Royal Society of Medicine and a member of the Association of American Physicians. During the years he was the Secretary-Treasurer of the American Board of Internal Medicine, he made outstanding contributions to the development of that Board at a time when the work of the Board was expanding most rapidly.

He has served the American College of Physicians as a Regent since April 1, 1944, and as a member of many of its most important and active committees. He served as First Vice President for the year 1948-1949 and was elected President-Elect at the New York Annual Session on March 31, 1949. He will assume office as President at the Thirty-First Annual Session to be held at Boston, Mass., during April 1950.

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### THE POSTGRADUATE COURSE PROGRAM OF THE AMERICAN COLLEGE OF PHYSICIANS

Since the Annual Session of the American College of Physicians in New York the latter part of March, four additional courses on the spring schedule have been concluded.

Course No. 5, "Electrocardiography: Basic Principles and Interpretation," was given at the Massachusetts General Hospital, April 25-30, 1949, under the Directorship of Dr. Conger Williams. The course, limited to 25 registrants, was filled to capacity and a large number of members could not be accommodated. Those who took the course have reported most enthusiastically upon its great worth.

Course No. 6, "Diseases Caused by Immune Mechanisms," was given under the combined auspices of the American College of Physicians and the University of Pittsburgh School of Medicine, at Atlantic City, April 28-May 1, 1949, under the Directorship of Dr. Leo H. Crip. This course also was registered to its capacity of 50, and although it was condensed into four days, those in attendance have indicated an unanimous and enthusiastic endorsement of all features of the course.

Course No. 7, "Cardiovascular Disease," was given in coöperation with various Philadelphia institutions and the American College of Physicians at the College Headquarters in Philadelphia, May 2-7, 1949, under the Directorship of Dr. William G. Leaman, Jr., F.A.C.P. Ninety-two physicians were registered, and the course was one of the most successful in this field the College has ever organized.

Course No. 8, "Physiological Basis for Internal Medicine," under the joint sponsorship of the American College of Physicians and the University of Pennsylvania Graduate School of Medicine, was given at Philadelphia, May 9-14, 1949, with a registration of 244 physicians. Obviously the instruction had to be of a didactic character with so large a group, but this course, regularly appearing on the College schedule, is probably the most popular course ever organized by the College. Dr. Julius H. Comroe, Jr., F.A.C.P., Professor of Physiology and Pharmacology in the University of Pennsylvania Graduate School of Medicine, was the Director.

Yet remaining on the spring schedule is Course No. 9, "Endocrinology," to be given at Tufts College Medical School, Boston, June 13-18, 1949, under the Directorship of Dr. Edwin B. Astwood, F.A.C.P. At the time of the preparation of this notice, there appears to be a wholly satisfactory registration developing. This course is designed for internists who are specially interested in Endocrinology and who desire further training in the basic physiology and biochemistry of the subject.

#### THE AUTUMN, 1949, PROPOSED SCHEDULE

The Advisory Committee on Postgraduate Courses and the Board of Regents have approved the following proposed schedule of courses for the autumn of 1949, but in not all instances have the directors accepted and the arrangements been concluded; neither have the dates in all instances been set. However, early in July the Postgraduate Bulletin will be published and mailed to all members and to all others requesting copies.

- (1) INTERNAL MEDICINE. One week; University of Minnesota Medical School; Dr. George N. Aagaard, Director of Postgraduate Education, and Dr. Cecil J. Watson, F.A.C.P., Director of the course.
- (2) PRECLINICAL SCIENCE IN INTERNAL MEDICINE. One week, October 24-29, 1949; Washington and St. Louis Universities, St. Louis, Mo.; Dr. Ralph A. Kinsella, F.A.C.P., and Dr. W. Barry Wood, F.A.C.P., Directors.
- (3) INTERNAL MEDICINE. One week; University of Wisconsin Medical School, Madison, Wis.; Dr. William S. Middleton, F.A.C.P., Director.
- (4) CARDIOLOGY. One week; Massachusetts General Hospital; Dr. Paul D. White, F.A.C.P., Dr. Howard B. Sprague, F.A.C.P., and Dr. Edward F. Bland, Co-Directors.
- (5) CARDIOLOGY. Two weeks; National Institute of Cardiology of Mexico, Mexico City; Dr. Ignacio Chavez, F.A.C.P., Director. This course may be delayed until sometime during 1950 and given as a summer course, in which the class will meet from 9:00 to 1:00 daily, and the rest of the day be free for vacation or other purposes.
- (6) CARDIOLOGY. One week; University of Southern California Medical School, Los Angeles, Calif.; Dr. George C. Griffith, F.A.C.P., Director. Dr. Griffith has accepted the directorship, but has not specified the date.
- (7) CLINICAL NEUROLOGY. One week, October 17-22, 1949; Jefferson Medical College of Philadelphia; Dr. B. J. Alpers, F.A.C.P., Director.
- (8) HEMATOLOGY. One week; Boston institutions. Dr. William B. Castle, F.A.C.P., has been requested to act as Director, but the course may have to be

delayed until sometime in 1950, due to autumn commitments which may interfere with Dr. Castle's organizing and directing the course.

- (9) GASTRO-ENTEROLOGY. One week; University of Chicago; Dr. Walter L. Palmer, F.A.C.P., Director.
- (10) PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE. One week; Tulane University of Louisiana School of Medicine, New Orleans, La.; Dr. George E. Burch, Jr., F.A.C.P., Director.

#### APPLICATIONS BEING RECEIVED FOR THE AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWSHIPS, 1950-1951

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1950 to June 30, 1951. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from \$2,200 to \$3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1949. Announcement of awards will be made November, 1949.

#### REGENTS OF THE COLLEGE TO AUTUMN MEETING NOVEMBER 12-13, 1949

President Reginald Fitz, Boston, has designated the date of November 12-13 for the next meeting of the Board of Regents of the American College of Physicians. The Credentials Committee will meet on November 11-12, and other important Committees will likewise meet on November 12.

Proposals of candidates for membership must be filed 60 days in advance of action. Therefore, September 12 is the closing date for receipt of proposals of candidates for action at this meeting.

#### ADDITIONAL LIFE MEMBERS

The American College of Physicians gratefully acknowledges recent subscriptions to Life Membership by the following Fellows of the College:

Walter L. Bierring, Des Moines, Iowa.  
William V. Conn, Greensburg, Pa.  
Robert M. Moore, Indianapolis, Ind.  
Arthur W. Phillips, Philadelphia, Pa.  
Clark P. Pritchett, Columbus, Ohio.  
Samuel J. Schneiersen, New York, N. Y.  
Clarence H. Webb, Shreveport, La.

#### SPECIALTY BOARD FORMED PREVENTIVE MEDICINE AND PUBLIC HEALTH

With approval received on February 6, 1949, from the Advisory Board of Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association, the American Board of Preventive Medicine and Public Health, Inc., began the work of certifying to the qualifications of physicians in these closely

related fields. Among the first officers of the new Board are the following Fellows of The American College of Physicians: Walter L. Bierring, M.D., Des Moines, Iowa; Felix J. Underwood, M.D., Jackson, Miss.; and James S. Simmons, M.D., Boston, Mass. Colonel Don Longfellow, (MC), U. S. A., F.A.C.P., and George R. Callender, M.D., F.A.C.P., Chief of the Pathology Division of the Veterans Administration, both of Washington, D. C., are Consultants to the Board from the Federal Services.

The membership of the Board represents the American Public Health Association, The American and Canadian Public Health Associations, The Association of Schools of Public Health, The Southern Medical Association, and the Section on Preventive and Industrial Medicine and Public Health of The American Medical Association, as well as practitioners of the specialties.

The Board is authorized to grant certification without examination to a "Founder's Group," defined to include Professors and Associate Professors of Preventive Medicine and Public Health in approved schools of Medicine or Public Health, or individuals who have been Presidents of the sponsoring societies, or practitioners who have had ten years or more of distinguished service in the field and are held to be eligible by the Board. Otherwise, certification is by examination. The requirements are as follows: moral and ethical standing; graduation from an approved United States or Canadian Medical School, or from a satisfactory foreign Medical School; an internship of one year or more in an approved or satisfactory hospital; licensure in the U. S. A. or Canada; special training in Preventive Medicine or Public Health, including at least six years of special training or practice in Preventive Medicine and Public Health, including at least one academic year of graduate study leading to the Degree of Master of Public Health, or a satisfactory equivalent, and field training or acceptable residency in the specialty of at least two years; limitation of practice to the teaching or practice of Preventive Medicine or Public Health.

Examinations will be in two parts; the first consisting of a comprehensive written examination; the second part being an oral or practical examination. Applications for examination must be filed with the Secretary of the Board at least 90 days before the date of examination on prescribed application forms accompanied by photographs of the applicant, letters of endorsement, and the application fee. The application fee is \$15.00, not returnable, and the certification fee is \$35.00.

The first examinations of the Board were held in Washington, D. C., May 14-16, 1949. The next examinations are scheduled to be held in New York City, October 22-24, 1949. Notices of future examinations will appear in this publication.

Requests for further information concerning the requirements and activities of the Board and applications for admission to examinations should be addressed to Ernest L. Stebbins, M.D., Secretary-Treasurer, The American Board of Preventive Medicine and Public Health, Inc., 615 N. Wolfe St., Baltimore 5, Md.

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The Chicago Medical Society will offer a course in **CARDIO-RENAL** and **PERIPHERAL VASCULAR DISEASES** October 17-22, 1949. The faculty will include leading teachers from all over North America and the course will comprise lectures, question periods, round tables, and informal conferences. The location will be Thorne Hall, Northwestern University Medical School, Chicago, and registration will be limited to 100. Information may be secured from Willard O. Thompson, M.D., F.A.C.P., Chairman, Committee on Postgraduate Medical Education, Chicago Medical Society, 30 North Michigan Avenue, Chicago 2, Ill.

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The American Trudeau Society coöperating with the University of Colorado School of Medicine will offer a Postgraduate course in **PULMONARY DISEASES** and

THORACIC ANESTHESIOLOGY at the University of Colorado Medical Center, Denver, July 18-30, 1949. Registration is limited to physicians from Colorado, North and South Dakota, Nebraska, Kansas, New Mexico, Arizona, Utah, Wyoming, and Montana, and to physicians who have a special interest in the subject of the course. The registration fee is \$100.00. A complete outline of the course, application blanks, and other information may be secured by writing to the American Trudeau Society, 1790 Broadway, New York 19, N. Y.

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#### THE KAPPA DELTA AWARD FOR RESEARCH IN ORTHOPAEDIC SURGERY

The National Council of the Kappa Delta Sorority has inaugurated a prize of \$1,000.00 to be given annually by the American Academy of Orthopaedic Surgeons for the best research in orthopaedic surgery performed during the year by an individual in the United States. The first award, for the year 1949, will be announced at the 17th annual convention of the Academy in New York, February 11, 1950. Those wishing to compete for this prize can secure further information from Dr. Walter Stuck, 1426 Nix Professional Bldg., San Antonio, Tex., Chairman of the Award Committee for 1949.

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#### COATESVILLE, PENNSYLVANIA, VETERANS ADMINISTRATION HOSPITAL RECRUITING RESIDENTS IN NEUROLOGY

Several openings are available in the residency training program in neurology at the Veterans Administration Hospital, Coatesville, Pa. The program, organized by the Philadelphia Deans Committee, has been approved by the American Medical Association. This residency covers a period of three years or less, depending on the previous experience of an applicant, and is designed to prepare residents for certification in neurology by the American Board of Psychiatry and Neurology. The program includes rotation through the Veterans Administration Hospital, Coatesville, Pa., Veterans Administration Regional Office, Philadelphia, and the Philadelphia General Hospital. Applications should be sent to the Manager, Veterans Administration Hospital, Coatesville, Pa.

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#### CANAL ZONE APPOINTMENTS OPEN

A limited number of Civil Service appointments are available in the Canal Zone for physicians interested in tropical medicine. The Panama Canal Health Department maintains a number of hospitals and dispensaries and supervises health conditions in the Zone as well as Colon and Panama City. There are excellent schools for the young. The beginning salary is \$5,599.00 a year, plus free transportation to the Canal Zone, for physicians graduated from approved medical schools who have completed a year's internship in an approved hospital and been licensed in a State, and who are able to pass a standard physical examination. A beginning salary of \$6,540.00 is offered to those who, in addition, have had a minimum of three years of medical practice.

A pamphlet, "The Panama Canal—Employment Information and Personnel Policies," may be had from the Chief of Office, The Panama Canal, Washington 25, D. C. Applications may be submitted to this officer or to the U. S. Civil Service Commission, Washington 25, D. C.



## THE PHILADELPHIA COUNTY MEDICAL SOCIETY CELEBRATES ITS CENTENARY

On Wednesday, May 11, 1949, the Philadelphia County Medical Society of Pennsylvania celebrated its 100th year at a meeting and dinner at the Bellevue Stratford Hotel in Philadelphia. Dr. Richard A. Kern, F.A.C.P., President of the Society, presided, and greetings were received from Dr. F. F. Borzell, F.A.C.P., Speaker of the House of Delegates of the American Medical Association, from Dr. Gilson Colby Engel, President of the Medical Society of the State of Pennsylvania, and from Dr. T. Grier Miller, F.A.C.P., President of the College of Physicians of Philadelphia. The address of the evening was delivered by the Honorable Lister Hill, United States Senator from Alabama.

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Dr. Spafford Ackerly, F.A.C.P., Professor of Psychiatry and head of the Department, University of Louisville Medical School, was one of the four taking part in the "Town Meeting of the Air" broadcast from Rochester, Minn., during Mental Health Week, in the latter part of April.

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Willard Cole Rappleye, M.D., F.A.C.P., has been appointed Vice President in Charge of Medical Affairs of Columbia University. Dr. Rappleye has been Dean for many years of the College of Physicians and Surgeons of the University.

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H. Corwin Hinshaw, Sr., M.D., F.A.C.P., formerly of the Mayo Clinic and Foundation, Rochester, Minn., has become Clinical Professor of Medicine in the Stanford University School of Medicine. Dr. Hinshaw's office will be located at 490 Post Street, San Francisco, Calif.

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The Medical Society of the State of North Carolina celebrated its sesquicentennial at the annual session in Pinehurst early in May. Paul F. Whitaker, M.D., F.A.C.P., Kinston, A.C.P. Governor for North Carolina, served as moderator of a panel discussion and Joseph S. Hiatt, Jr. (Associate), McCain, N.C., was moderator of the symposium. The guest speaker was Hugh J. Morgan, M.D., F.A.C.P., Nashville, Tenn., 1947-48 President, whose subject was "Then and Now."

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Aldrich C. Crowe, M.D., F.A.C.P., Ocean City, N. J., was made President-Elect of The Medical Society of New Jersey at the Society's recent meeting at Atlantic City. Sigurd W. Johnson, M.D., F.A.C.P., Passaic, and Harrold A. Murray, M.D., F.A.C.P., Newark, were elected First and Second Vice Presidents, respectively.

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Brig. General James F. Simmons, (MC), U. S. A., Ret'd, F.A.C.P., Dean of the Harvard School of Public Health, and President of the Association of Schools of Public Health, has been elected Chairman of the Advisory Medical Board of the Leonard Wood Memorial of the American Leprosy Foundation. Dr. Simmons was recently awarded the Legion of Honor of the French Government recognizing his contributions during the war as Chief of the Preventive Medicine Service of the U. S. Army.

*OBITUARIES*

## DR. W. HALSEY BARKER

On March 26, 1949, Dr. W. Halsey Barker, son of the late Dr. Lewellys F. Barker, died following a long illness at the Johns Hopkins Hospital.

Dr. Barker was born January 3, 1907, graduated from Princeton University with an A.B. degree in 1928, and entered that fall the Johns Hopkins University School of Medicine, from which he graduated in 1932. He served as House Officer at the Johns Hopkins Hospital from 1932 to 1935 and, after serving on the Staff of the Hospital of the Rockefeller Institute for Medical Research from 1935 to 1937, returned in 1937 as Resident in Medicine and later became Assistant Physician and Physician-in-Chief of the Clinic for Gastro-Intestinal and Nutritional Disorders.

Appointed Instructor in Medicine in the Johns Hopkins University School of Medicine in 1937, Dr. Barker became Assistant Dean in 1938 and Assistant Professor of Medicine in 1941.

Dr. Barker was elected to Associateship in the American College of Physicians in 1939, and to Fellowship in 1944. From 1942 to 1947 he served capably as Assistant Editor of the *ANNALS OF INTERNAL MEDICINE*. He was also a member of The Harvey Society, the American Clinical and Climatological Association and the American Medical Association.

Dr. Barker was an indefatigable worker, conscientious, and admired by all his friends. It is with a great sense of loss that we acknowledge his death; his place in our ranks will be difficult to fill.

WETHERBEE FORT, M.D., F.A.C.P.,  
Governor for Maryland

## DR. ALBERT RANKIN MARTIN

Dr. Albert Rankin Martin, of Chicago, Ill., died October 13, 1948.

Dr. Martin was born at Leer, Holland, in 1862. He graduated from Rush Medical College in 1892, and for many years served as Staff Physician at the St. Mary of Nazareth and Henrotin Hospitals in Chicago. He was a member of the Chicago Medical Society, the Illinois State Medical Society, the American Medical Association, and of the old American Congress on Internal Medicine, by virtue of which membership he became an Associate of the American College of Physicians in 1920.

## DR. NATHANIEL EMMONS PAINE

Dr. Nathaniel Emmons Paine was born July 14, 1853, and died November 30, 1948, at the age of 95 years. He had been a Fellow of the American College of Physicians since 1920.

After graduating from Albany Medical College in 1875, Dr. Paine spent a year in postgraduate study in Vienna, and soon thereafter became interested in psychiatry. He was an assistant physician at the Middletown State Hospital for some years, and was Professor of Psychiatry of Boston University School of Medicine from 1887 to 1925, when he retired. Dr. Paine was a clear lecturer and a good teacher, and his students developed a real affection for him. His students knew that he always had a great and sincere interest in them.

Aside from his interest in medical teaching and the practice of psychiatry, he was the author of several books on genealogy, and received the Certificate of Merit in Genealogy of the Council of the Institute of American Genealogy in 1939.

Dr. Paine had a long and useful life, devoted to his specialty and to the training of young men who are following him in the important field of psychiatry.

## DR. WILLIAM A. PLUMMER

Dr. William A. Plummer, of Rochester, Minn., died March 22, 1949.

Dr. Plummer was born June 30, 1883, at Racine, Minn. He received the degree of M.D. in 1910 from Northwestern University. He entered the Mayo Clinic as assistant in medicine in June, 1910, and became head of a section in medicine February 1, 1917. Later, he became associate professor of medicine in the University of Minnesota (Mayo Foundation), and senior consultant in a division of medicine of the Mayo Clinic. He was a fellow of the American College of Physicians (1928), and a member of the Minnesota Society of Internal Medicine, the Central Society for Clinical Research, the American Association for the Study of Goiter, the Association for the Study of Internal Secretions, the Southern Minnesota Medical Association, the American Medical Association and Sigma Xi.

Among William A. Plummer's outstanding characteristics were his kindness and his friendliness to his patients and to his associates. He was an astute clinician and made many clinical observations of importance. Because of his retiring nature, he was more likely to impart these observations by word of mouth than through his writings. In this way he laid the foundation for many investigations, which he was glad to have carried out by others. His major interest, as was that of his brother, Henry S. Plummer, was in the field of thyroid disease, but his knowledge and ability in the clinical practice of medicine, generally, were very wide. He was unusually skilled in his observations on patients and carried their problems in his mind constantly until they were solved. His intense absorption in the problems of his patients was balanced by a fine sense of humor. He had keen insight into the psychological reactions of his patients and, also, those of his associates. This aided in giving him unusually good judgment in relation to the problems of the practice of medicine.

EDGAR V. ALLEN, M.D., F.A.C.P.,  
Governor for Minnesota

## DR. FREDERICK ERASTUS WARD

Dr. Frederick Erastus Ward, of Easton, Pa., died at his home on May 4, 1949.

Born in 1882, Dr. Ward attended Lafayette College and graduated from the Medico-Chirurgical College of Philadelphia in 1906.

Dr. Ward had civic as well as medical interest and was a former City Councilman of Easton. He had also served as Medical Inspector of the Public Schools of his home city, Chief of Staff of the Pennsylvania State Clinic for Tuberculosis, and the Baby Clinic of the Visiting Nurses' Association.

Dr. Ward was a member of his County and State Medical Societies and of the American Medical Association. In 1924 he was elected to membership in the American Congress on Internal Medicine and through this became an Associate of the American College of Physicians.

THOMAS M. McMILLAN, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

## DR. ROBERT OSGOOD BROWN

The untimely death of Robert Osgood Brown, M.D., F.A.C.P., on February 1, 1949, is a tragic loss to his professional colleagues and his many friends.

Dr. Brown was born February 13, 1890, in Chicago, Ill. He received his B.S. degree from the University of Chicago in 1912, and was graduated from Rush Medical College in June, 1914, interning at Cook County Hospital, Chicago, until June, 1916. He was an officer in the National Guard and served with the Pershing Expedition on the Mexican Border in 1916. He entered the practice of Medicine in Santa Fe, N. M., in 1916, specializing in internal medicine and diseases of the chest.

He became a Fellow of the American College of Physicians in 1932, and served as College Governor for New Mexico from 1942. He was also a Fellow of the American Medical Association and of the American College of Chest Physicians, and a member of the American Heart Association, American Trudeau Society and the New Mexico Clinical Society.

Dr. Brown was prominent in medical and civic affairs in New Mexico. He was formerly Associate Medical Director of Sunmount Sanatorium, staff member of St. Vincent Sanatorium and Hospital, founder and member of the Board of Directors of The Santa Fe Clinic and Foundation for Research and Treatment of Cancer, Santa Fe. He was actively interested in public health and welfare work in New Mexico, having served as Chairman of the New Mexico Public Welfare Board, Medical Consultant to the New Mexico Department of Public Welfare, and as Chairman of the Legislative Committee of the State Medical Society.

He was President of the Santa Fe County Tuberculosis Association at the time of his death; and had been President of the New Mexico Medical Society, and of the New Mexico Tuberculosis Association. The latter Association adopted the following Minute.

"Whereas Doctor Robert O. Brown's outstanding career in medicine and his untiring efforts to improve the health, social and economic welfare of his fellow citizens are matters of permanent record in the annals of New Mexico,

"Be it resolved that the New Mexico Tuberculosis Association and all its affiliated associations will ever remember and forever be indebted to Doctor Robert O. Brown for his untiring efforts in his official capacity as president from 1934 to 1937; his active participation as a member of its board of directors; his leadership and guidance in establishing the State Department of Public Health; his wise leadership as president of the Santa Fe County Tuberculosis Association and his capacity for friendship and personal interest in the problems, the welfare and the success of his fellow men."

Dr. Brown enjoyed an extensive and active practice. The community, his patients and his host of medical friends throughout the Southwest mourn his untimely death. We have lost a great and good friend and Doctor.

CARL H. GELLENTHIEN, M.D., F.A.C.P.

#### DR. ALPHONSE E. WALCH

Dr. Alphonse Edmund Walch of Minneapolis, Minn., a fellow of the American College of Physicians since 1942 and a diplomate of the American Board of Internal Medicine, died November 14, 1948, at the age of 42. Dr. Walch was a graduate of St. Mary's College, Winona, Minn., and of the St. Louis University School of Medicine. He was a member of the medical staffs of the Abbott, Minneapolis General and St. Mary's Hospitals.

#### DR. JAMES MURRAY WASHBURN

Dr. James Murray Washburn, Associate Professor of Medicine Emeritus of Northwestern University, died of carcinoma of the stomach on January 16, 1949, in his seventy-fifth year, at Lake Lure, N. C.

Dr. Washburn was born in Chicago on December 6, 1873. He received an A.B. degree from Harvard University in 1895, and an M.D. degree from Northwestern University Medical School in 1899. He was appointed a member of the Rush Medical College faculty in 1904, in which capacity he served until 1929, attaining the rank of Assistant Clinical Professor of Medicine. He served in the Army Medical Corps in World War I; when discharged, he held the rank of Lieutenant Colonel. From 1929 until 1934, he was an Associate Professor of Medicine at Northwestern University. From 1907 until 1929, he was a member of the Associate Staff of Presbyterian Hos-

pital. For many years, prior to the association of the Passavant Memorial Hospital with Northwestern University, he served on the staff of this institution and was a leader in the movement to reestablish the Passavant Memorial Hospital in close affiliation with Northwestern University. In 1927, Dr. Washburn was elected Chief of Staff, a position to which he was reelected annually until his retirement from practice in 1934.

Dr. Washburn was elected a Fellow of the American College of Physicians in 1934. He was also a Fellow of the American Medical Association, and a member of the Institute of Medicine, Chicago, the Chicago Society of Internal Medicine, and the Illinois State Medical Society. He was a past President of the Rutherford County, N. C., Medical Society.

Modest and unpretentious, James Murray Washburn was an able clinician and teacher, and a delightful companion with a droll sense of humor. Upon retirement from active practice in 1934, he moved to Lake Lure, situated in the Blue Ridge Mountains of North Carolina, where he had a summer home. He transformed this into the "Chalet Club" which became popular with people seeking beautiful scenery and rest.

His patients worshipped him and continue to complain that they cannot find anyone to take the place of this wise physician who believed that a specialist in Internal Medicine could render more satisfactory and effective service if he were also the "family doctor." His genial manner and kindly disposition will be missed by his colleagues and his many friends.

HOWARD B. CARROLL, M.D., F.A.C.P.

#### DR. OTTO ANDREW GEORGE REINHARD

Dr. Otto A. G. Reinhard, internist of Lincoln, Nebr., died on February 12, 1949. He was born in 1897 at Cullom, Ill., attended Wartburg Academy at Clinton, Iowa, and received from the University of Illinois the degrees of Bachelor of Science, 1920, and Doctor of Medicine, 1923. During World War I, he was a member of the Illinois Medical Units, S.A.T.C.

Following his internship in the Cook County Hospital, Chicago, in 1923-1924, Dr. Reinhard served the Public Health Division of the Rockefeller Foundation for three years as Siamese Field Director. He then became a member of the Lincoln Clinic, Lincoln, Nebr., and served it until his death. He also held staff appointments to the Bryan Memorial and Lincoln General Hospitals. He was a diplomate of the American Board of Internal Medicine.

Dr. Reinhard was elected to Fellowship in the American College of Physicians in 1937. He was also a fellow of the American Medical Association, and a member of the American Heart Association, Association for the Study of Internal Secretions, Nebraska State Medical Association, and Lancaster County Medical Society.

J. D. MCCARTHY, M.D., F.A.C.P.,  
Governor for Nebraska

#### DR. SAMUEL B. SCHOLZ

Samuel B. Scholz, M.D., F.A.C.P., was born in Dunn County, Wis., March 29, 1878, and died in Jenkintown, Pa., March 4, 1949.

Dr. Scholz attended Purdue University, the University of Michigan Medical School, for two years, and then the Denver and Gross College of Medicine, from which he received his M.D. degree in 1905. The field of Insurance Medicine can feel justly proud to have had Dr. Scholz enter it in 1907. He served in the Medical Department of the Equitable Life Insurance Society, 1907-17; as Medical Director of the Missouri State Life Insurance Company, from 1917 to 1919; as Associate Medical

Director of the Massachusetts Mutual Life Insurance Company, from 1919 to 1930; and as Medical Director of the Penn Mutual Life Insurance Company, Philadelphia, from 1930 until retirement in 1948.

Dr. Scholz was a Fellow of the American College of Physicians, since 1935, and of the American Medical Association. He was a former President of the Association of Life Insurance Medical Directors of America and Vice President of the International Life Insurance Medical Congress, 1938-1939. He also was a member of the Philadelphia and American Heart Associations.

Dr. Scholz was indeed a very fine and able physician and will be greatly missed by all who know him.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

#### DR. ADOLPH EMIL VOEGELIN

On February 22, 1949, Dr. Adolph E. Voegelin, of Detroit, Mich., died suddenly in his office. Dr. Voegelin was born in Philadelphia in 1894. He received his Bachelor's degree from Central High School, and his M.D. degree in 1916 from the Medico-Chirurgical College of Philadelphia. He became a Fellow of the American College of Physicians in 1924, and later a diplomate of the American Board of Internal Medicine. Dr. Voegelin's interest was chiefly in cardiology, and at the time of his death he was Chief of Staff of the Evangelical Deaconess Hospital, in Detroit, and Chief Cardiologist to the same institution.

DOUGLAS DONALD, M.D., F.A.C.P.,  
Governor for Michigan

# ANNALS OF INTERNAL MEDICINE

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